COMORBIDITY OF MENTAL DISORDERS

ASSOCIATION WITH THE SEROTONIN TRANSPORTER GENE

POLYMORPHISM IN A COMMUNITY SAMPLE

by

Ruben Miozzo, MD MPH

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ABSTRACT

This proposal had three interrelated aims. The first aim was to examine the lifetime prevalence and comorbidity of selected mental disorders in a group of 847subjects sampled from the Epidemiologic Catchment Area (ECA). The second aim was to examine the association of the Serotonin Reuptake (SERT) gene polymorphism with the prevalence, comorbidity burden of psychopathology in this sample. The final and third aim, born out of the need to fulfill the first two goals, was to develop instruments to quantitatively and comprehensively measure the comorbidity burden in a sample.

We found extensive comorbidity between the individual anxiety disorders, between the anxiety and mood disorders, and between mood disorders and Alcohol Dependence. Agoraphobia, Social Phobia, Obsessive Compulsive Disorder (OCD), Generalized Anxiety Disorder (GAD) were highly comorbid with each other. Comorbidities between Major Depressive Disorder (MDD) and Panic Disorder (OR: 3.20), Agoraphobia (OR: 2.79), Social Phobia (OR: 2.46), and, OCD (OR: 4.74) were highly significant.

Using Poisson Regression models, we found an increased risk for lifetime prevalence of Panic Disorder in participants who were carriers of the short (s) allele of the SERT polymorphism (Prevalence Ratio: 2.61). We found a significant association between SERT (s) allele carrier status and a decreased risk to be diagnosed with Obsessive-Compulsive Disorder in the time-to-event analysis (Hazard Ratio: 0.11). In addition, the carriers of the SERT (s) allele had a significant increased risk for two comorbidity pairs, MDD and Social Phobia, and Agoraphobia and MDD.

When comparing the overall number of diagnoses, we were unable to find an increase in the burden for psychopathology in the carriers of the (s) allele. In summary, the SERT polymorphism seems to confer a modest vulnerability to psychopathology.

We explored the relationship between the number of individuals diagnosed, the number of diagnoses and the number of comorbidities, both for the individual mental disorders, as well as for the whole sample. Using simple probability concepts, based on discrete random variables, we developed a series of instruments to measure the comorbidity burden in our study sample. These instruments could be useful in the comparison of the diagnostic information between samples.

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Thesis Committee

Joe Bienvenu, MD PhD

William Eaton, PhD

Charles Flexner, MD

Alternate Members:

N. Franklin Adkinson, MD

Adam P. Spira, PhD

In a Personal Note:

Mayra, thanks for all your love and support

Thanks to all my family and friends for being there for me

CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER 01: INTRODUCTION

C01.P01 Overall Aims:

In the study, we investigated the association between the serotonin transporter gene (SERT) polymorphism and the prevalence, comorbidity burden, time to diagnosis, age of onset, and treatment patterns of Alcohol Dependence, Alcohol Abuse, Opioid Dependence, Schizophrenia and other Psychotic Disorders, Major Depressive Disorder, Bipolar Disorder, Panic Disorder, Agoraphobia, Social Phobia, Obsessive Compulsive Disorder, Generalized Anxiety Disorder, Simple Phobia, Dysthymic Disorder, and Anxiety Disorder Not Otherwise Specified. These conditions were the most frequently diagnosed mental disorders in a group of 847subjects sampled from the Epidemiologic Catchment Area (ECA) in Baltimore, Maryland.

The primary goal of our study was to examine the phenomenon of comorbidity between the mental disorders. Extensive comorbidity between mental disorders presents a major challenge to our current psychiatric nomenclature as well as a hindrance to the advancement of research in the etiology and treatment of mental disorders.

Our approach was innovative and comprehensive. We proposed indicators of the comorbidity burden that allow us to characterize and quantify this phenomenon both for the whole sample, as well as for the individual mental disorders included in the analysis.

We explored the association between a specific polymorphism in the serotonin transporter gene (SERT) and the increase in the prevalence and co-occurrence (comorbidity) of these aforementioned mental disorders. The SERT gene polymorphism has been extensively

studied for potential associations with a variety of mental disorders. The findings have been, so far, inconclusive.

In addition, we analyzed the age- at-onset of the individual mental disorders, and we - investigated whether the carriers of the SERT short (s) allele had a significant difference in the time to attain full criteria for the selected disorders as compared to the non-carrier subjects.

Lastly, we analyzed the use of medications in the study participants. We explored whether the carriers of the SERT (s) allele had an increase in the use of psychotropic agents, as compared to the non-carrier subjects.

C01P02. Summary

We examined the burden of comorbidity in our study sample using novel techniques. We determined whether there is an association of the SERT (s) gene polymorphism with an increased prevalence and comorbidity, a shortened time to attain a diagnosis, and an increase in the use of psychotropic medications

The value and novelty of this work was that we were able to evaluate the comorbidity of several mental disorders in a comprehensive way in a study sample that was obtained from the community using probabilistic methods. The study participants were assessed by board certified psychiatrists, trained in the use of the Schedules for Clinical Assessment in Neuropsychiatry. The use of this rich population based sample that has been comprehensively examined and genotyped afford us this unique opportunity to assess the patterns of psychiatric comorbidity, as well as the potential impact that the SERT polymorphism conveys in the overall psychopathology.

CHAPTER 02: REVIEW OF COMORBIDITY IN MENTAL DISORDERS

C02.S01 Background and Significance of Comorbidity in General Medicine

Comorbidity has become an important area of study in medicine. Over the past decades, there has been an increased interest in the phenomenon of comorbidity. This interest is fueled by the awareness that individuals are frequently affected by more than one disease or condition. It is safe to say that, in most clinical settings, the management of patients with multiple coexisting conditions is more the norm rather than the exception. (C2R01-02).

Comorbidity cannot be reduced to a mere issue of frequency or prevalence in a clinical sample or group of individuals under examination. It is well recognized that the presence of multiple medical conditions in an individual could greatly impact clinical symptoms, the diagnostic process, the overall prognosis, and the clinical management of the conditions under treatment. Comorbidity has a strong impact on mortality, health-related quality of life, and overall daily functioning (C2R03-07). In addition, comorbidity has a substantial effect on health care expenditures. As an example, it is estimated that 80% of Medicare expenditures in the United States are devoted to patients with four or more chronic conditions (C2R08).

C02.S02. Concept of Comorbidity in Medical Literature

In spite of the strong impact that comorbidity imparts on virtually all aspects of public health, it is a surprisingly recent and poorly defined concept in the medical literature. Alvan Feinstein coined the term comorbidity in 1970 (C2R09). He defined it as: "any distinct additional

clinical entity that has existed or that may occur during the clinical course of a patient who has the index disease under study"

C02.S03. Classification of Comorbidity

In 1974, Kaplan and Feinstein further formulated and clarified the concept of comorbidity (C2R10). These authors described four different types of comorbidity that they branded: diagnostic comorbidity, pathogenic comorbidity, prognostic comorbidity and cogent comorbidity.

Diagnostic comorbidity applies when a particular symptom of a disease occurs in a patient with two coexisting conditions that independently could cause said symptom. The authors give the example of polyuria in a patient that suffers from both diabetes mellitus (the index condition) and a co-existing renal disease (the comorbid condition). As the index condition (diabetes) and the comorbid condition (renal disease) produce polyuria, it is expected that the prevalence of polyuria will be higher in patients affected both with diabetes and renal disease when compared to the ones affected solely with diabetes. Thus, diagnostic comorbidity can aid with the disease definition and symptom prevalence by examining how symptoms of a disease are impacted by the presence of additional diseases to the index condition under study.

Pathogenic comorbidity describes the presence in a patient of a second disease that is considered "related" to the index condition. The authors state that certain cardiovascular or renal disorders can be regarded as "related" to diabetes (index disease), while other cardiovascular diseases can be regarded as "unrelated". Thus, pathogenic comorbidity can serve as a framework to investigate or to describe how one index disease can be the etiological risk factor for a second disease. It is important to note that the authors believed that not all comorbidities should be considered etiologically "related". Thus, the finding in a sample of a

high co-occurrence of two conditions could be seen as an indicator of a potential common etiologic link, but not as a proof of one.

Prognostic comorbid applies when "an ailment predisposes, either by itself or in combination with the main disease, to the future development of adverse target events". As an example, the authors state that "a patient with diabetes and hypertension may be more likely to develop retinopathy than a patient with diabetes alone". Similarly, "a diabetic patient with chronic obstructive pulmonary disease may be more likely to develop cardiac decompensation than if the lungs were normal". This concept seems similar to the concept of pathogenic comorbidity, as it postulates the etiological risk factor involved in comorbidity. The difference is that is stresses the importance of temporality, that is that the third condition develops later in time as the consequence of the first two conditions.

Kaplan and Feinstein coined the term cogent comorbidity to describe a scenario where the additional ailment "might be expected to impair a patient's long-term survival". Cogent comorbidity is present in this definition if the added conditions "involved vital body systems or were associated with anatomic, functional, or behavioral effects that might either threaten life directly or make the patient particularly susceptible to fatal ailments". Non-cogent comorbidity would describe other scenarios where additional ailments have no impact on survival, specifically "the term non-cogent was applied to chronic conditions that could be well controlled with or without medication and that had no direct effects on vital organs. Another type of non-cogent comorbidity consisted of episodic events that had occurred once in the past, without involvement of heart or brain, and without residua in the affected structures".

C02.S04. Additional and Novel Classifications

In 1999, Angold et al. (C2R11) proposed several additions to the classification of the comorbidity phenomena that are relevant to the field of mental illness. The most important additions were the concept of homotypic comorbidity and concurrent or successive comorbidity. Homotypic comorbidity describes the case of co- occurrence of two or more disorders within the same diagnostic grouping. Heterotypic comorbidity defines the presence of two disorders that do not belong to the same diagnostic grouping. The term grouping used by these authors stems from the classification in psychopathology, where mental disorder are placed in groups due to their shared symptoms (e.g., anxiety disorders, psychotic disorders). The authors gave the example of major depression and dysthymia as an illustration of homotypic comorbidity and, major depression and conduct disorder as an example of heterotypic comorbidity, respectively. The authors suggested that homotypic comorbidity may be a possible indicator of the lack of validity of individual diagnostic categories. In the example given, the homotypic comorbidity between major depression and dysthymia might suggest that the diagnostic criteria for these disorders are poorly defined at a symptom level. Thus, the current classification system could be splitting one disorder into two distinct conditions. An alternative explanation would be that homotypic comorbidity is an indicator of how the diagnostic criteria of a particular disorder could fail to capture the continuity of a single disease process over time with its natural waxing and waning (primary dysthymia that over time can worsen to major depression, or major depression that can, over time, improve to a milder, albeit chronic form).

In addition, Angold et al. (C2R11) also posited the concept of concurrent versus successive comorbidity. Concurrent comorbidity applies to the existence of a co-occurrence of two or more diseases at the same time, whereas successive comorbidity describes the case where one person is affected first by one disease, and later on by a second disease, but the two diseases never affect the subject at the same time.

C02.S05. Primary versus Secondary Disorder Distinction

The concept of concurrent versus successive comorbidity is analogous to the distinction of primary versus secondary disorder (C2R14). If an individual is diagnosed with two disorders, the diagnosis that came first in time is considered the primary disorder. In this case, the primary-secondary disorder distinction is used in a pure chronological approach. The primary vs. secondary distinction can also be used in an etiological framework. In this case, the primary condition is considered the cause of the secondary diagnosis. This etiologic distinction between primary and secondary is used in the DSM-III organic disorders (due to medical condition), and substance induced disorders (C2R12). The third use of the primary versus secondary disorder distinction applies to the case of symptom or diagnostic hierarchy (C2R14). In this use, the subject presents with multiple symptoms that could fit into two diagnoses, and the condition that has a hierarchical precedence gets diagnosed at the cost of the second. As an example, a patient might present with severe delusions, auditory hallucinations, panic attacks, and insomnia. The clinical judgment and hierarchical rules of the psychiatric classification points out to one diagnoses as primary (psychosis). A secondary diagnosis of anxiety or sleep disorder might be withheld as these "secondary" symptoms might subside once the psychosis is managed.

C02.S06. Comorbidity and Longitudinal Course of Psychopathology

The concurrent versus successive or the primary versus secondary paradigms are connected to the longitudinal study of psychopathology. The study of the course of psychopathology over time is an important concept when analyzing the phenomenon of comorbidity. The study of the "natural history of psychopathology" as postulated by Eaton (C2R15) has a particular relevance in mental illness, as psychiatric disorders are usually

assessed based on their lifetime prevalence. An examination of the onset, course and outcome of the mental disorders in a population-base sample is necessary to avoid the Berkson bias (C2R16) observed more in treatment samples, especially if the analysis is done in a cross-sectional approach. The relevance of the presence of two conditions in a lifetime prevalence measurement cannot be fully understood without an analysis of the dynamics between these two conditions over time.

C02.S07. Discussion and Summary

All the described definitions of comorbidity are largely theoretical and difficult to apply empirically. They reveal in an implicit way, several distinctive perspectives from where to examine the concept of comorbidity. The first vantage point addresses the identification of common casual factors, and mechanisms of action between the two comorbid conditions. The second perspective focuses on the level on which the assessment of the comorbidity is implemented: specifically, whether comorbidity is considered only as the co-occurrence of diseases in an individual, or as the presence in a person of a particular symptom that could be better explained as the effect of more than one disease.

In summary, the concept of comorbidity in medicine presents a challenge in an era of aging populations and increased use of technologies. In a narrow use, it is a descriptive term that defines the co-occurrence of multiple symptoms or diseases in the same individual. In a wider context, it can be seen as an indicator of common etiology, worsened prognosis, or therapeutic challenge.

C02.S08. Introduction to Comorbidity in Mental Health

The concept and study of comorbidity in mental disorders takes a dimension that is different from the rest of the medical field. There are many reasons that conspire to create this unique phenomenon (C2R14). One of these factors stems from the complex relationship between the mental and the physical or also called "medical" disorders.

C02.S09. Medical Comorbidity and the Diagnostic and Statistical Manual of Mental Disorders

The multiaxial diagnostic system represented a concerted effort from the DSM system in recording any possible medical condition that could cause or influence the course of the psychiatric disorder under study. The inclusion of medical conditions in the psychiatric diagnoses created numerous challenges. There was a lack of clear guidelines about the relevance of the medical conditions that should be included in the multiaxial diagnoses. In addition, there was a scarcity of specifiers in the system to document whether the medical conditions included in the multiaxial diagnosis played any role in the comorbid psychiatric disorders (except for the limited listing of mental disorders that were deemed completely due to a general medical condition). Nevertheless, this effort in detecting and recording medical comorbidities increased the awareness of the importance of the co-occurrence of psychiatric and medical conditions

C02.S10. Comorbidity and the Heterogeneity of Concepts of Mental Illness

Another rationale for this complexity stems from the challenges in the classification of mental disorders: in particular, the relationship between primary mental, also known as "clinical" disorders (e.g. schizophrenia, depression), substance use disorders, and personality disorders. A modern classification of mental disorders needs to provide coverage for all these conditions. Unfortunately, including heterogeneous dimensions in one single classification translates into a major challenge for its internal consistency.

When a psychiatric classification that contains heterogeneous concepts of mental illness is used to diagnose a patient, these heterogeneous concepts act as different perspectives from where to evaluate the diagnosed subject. The presence of different perspectives increases the likelihood that an individual can receive more than one diagnosis. Thus, the presence of heterogeneous concepts within a classification system constitutes a de facto source of comorbidity that is built into the classification.

The phenomenon of comorbidity in mental disorders is intimately linked to the development of the classification of mental disorders. It is therefore, necessary to review the historical development of the current classification of mental disorders to understand how this connection between comorbidity and classification developed over time.

C02S11. Comorbidity and Classification of Mental Disorders

The introduction of the third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III) (C2R12) in 1980 was a landmark as it inaugurated a new era in psychiatry. The DSM-III had three main areas of innovation. It established explicit diagnostic criteria, a multiaxial diagnostic assessment system, and an approach that attempted to be neutral with respect to the etiology of mental disorders.

C02S12. Historical Development of the DSM

The implementation of explicit diagnostic criteria was the result of a movement in psychiatry that started in the late 1960's.This movement, described by Klerman as neo-Kraepelinian (C2R13, 14), was fueled by a growing discontent of clinicians and researchers regarding the absence of objective, and empirically based methods for describing psychopathology. This neo-Kraepelinian group lead by Robins, Guze and their colleagues at Washington University in St. Louis, promoted a descriptive approach to psychopathology that was a refinement and extension of a categorical diagnoses model for major mental disorders advocated by Emil von Kraepelin. (C2R13, 14, 17).

C02S13. The Feighner Criteria

This group carried out extensive work on constructing and validating the diagnostic criteria and developing psychiatric interviews for research and clinical uses. The result of this work was the creation of the first diagnostic system with explicit criteria attached to every diagnosis. This criteria set was called "Feighner Criteria" (FC), for the first author of its publication (C2R18).These diagnostic criteria were largely based on the principles established by Robins and Guze, in their seminal paper discussing the establishment of diagnostic criteria for schizophrenia (C2R19). The basic tenet behind this classification was that, ultimately, each particular clinical syndrome would be validated by its clear separation from other disorders, would have a particular clinical course, as well as a specific genetic aggregation found in family studies.

The purpose of the use of explicit diagnostic criteria was to improve the reliability of the diagnosis of mental disorders for use in research. This improved reliability would work as a

stepping stone in the process of investigating the causes and clinical management of mental disorders.

The FC included 15 specific diagnostic groups: neuroses (anxiety, phobic, obsessional, hysterical disorders), affective disorders (depressive or bipolar disorders), schizophrenia, organic brain syndromes, substance abuse disorders (alcoholism, other drugs), sexual disorders (homosexuality, transsexuality), eating disorders (anorexia, bulimia), and one personality disorder (antisocial personality) (C2R17). Eli Robins, Samuel Guze and their colleagues expected that their newly created diagnostic criteria would allow assignment of about 80% of all psychiatric patients to one diagnosis (C2R17). Eli Robins frequently emphasized that the aim of their approach was to diagnose an individual with only one mental disorder. If one subject met criteria for more than one disorder, the subject should be considered as undiagnosed, or as having an uncertain diagnosis. The expectation for this 20% of undiagnosed subjects was to develop new diagnostic categories that would eventually diagnose these subjects in a valid fashion (C2R17).

C02.S14. Research Diagnostic Criteria and DSM

Based upon the success of the FC, Spitzer et al. elaborated the "Research Diagnostic Criteria" (RDC) at Columbia University, New York (C2R20). The RDC continued the use of explicit diagnostic criteria, providing coverage to an increased number of mental disorders.

Robert Spitzer later became the chair of the American Psychiatric Association's task force in charge of the development of the third edition of the DSM (DSM-III). The concepts that shaped the FC and RDC became the blueprint for the development of the DSM-III. The DSM-III extended the explicit diagnostic criteria to several additional diagnoses, and added a multiaxial diagnostic assessment system (C2R12).

C02.S15. The Multiaxial Diagnostic Assessment

The multiaxial diagnostic assessment was designed to separate the so-called "clinical disorders", such as schizophrenia or depression, from the effect of personality disorder traits or mental retardation when examining an individual's behavior. The distinction, largely influenced by political motivations, aimed at the importance of the evaluation of character and personality in the overall psychiatric assessment. However, the multiaxial diagnostic system had the unintended effect of promoting multiple diagnoses by default (C2R14, 17).

C02.S16. Elimination of Hierarchical Rules

Although the original FC had some hierarchical rules between disorders that prevented multiple diagnoses. The DSM-III purported a "cause-neutral" paradigm. This approach would lead to the removal of hierarchical barriers between the clinical disorders that were present in previous diagnostic instruments. There was a further elimination of additional exclusion criteria in the newer revisions of the DSM after the realization that mental disorders that were considered not etiologically related could be largely comorbid (C2R21).

C02.S17. The New Era of Comorbidity in Mental Disorders

The overall effect of the increase in the number of diagnostic categories, and the elimination of the exclusion criteria transformed the practice of psychiatric diagnosis over the following decades. Diagnosing a patient with multiple diagnostic labels became the norm rather than exception. However, not all psychiatric comorbidities should have the same consequence in our understanding of the mental disorders or in the coherence or validity of the classification.

Since the introduction of the DSM-III, and until the recent removal of the multiaxial classification in the fifth edition of the DSM, patients could be diagnosed on the Axis I with a clinical diagnosis (e.g. depression or anxiety). In addition, patients could be diagnosed in Axis I with a substance abuse disorder. Alternatively (or additionally), the same subject could be diagnosed with a personality disorder in the Axis II. These three diagnoses might be considered as three different mental disorders, or complementary perspectives from where to label the manifestations of a single ailment.

C02.S18. Heterogeneity of the Comorbidity in the Diagnostic Assessment

While the presence of a comorbidity between a mental disorder in Axis I and a medical condition in Axis III could be a desired phenomenon, the presence of a comorbidity between a "clinical disorder" and a substance abuse disorder or a personality disorder could be seen as the indicative of the heterogeneity of the concept of what constitute a mental disorder in the classification. The inclusion of these heterogeneous concepts translated into the existence of different approaches or viewpoints from where to diagnose a patient.

In contrast, the presence of strong patterns of comorbidity between the Axis I "clinical disorders', especially those that we could described as heterotypic, or belonging to different diagnostic classes like anxiety and depression, presents as a challenge to the underlying validity of the DSM categorical diagnostic system as a whole.

In practical use, when patients present both symptoms of depression and anxiety, a clinician might be inclined to diagnose the patient only with the former, in the belief that depression has a superior hierarchical position. Another clinician might be inclined to diagnose the patient only with an anxiety disorder, and a third with both. When a patient receives multiple diagnoses, different mental health practitioners might choose one diagnosis over the other,

depending on their current assessment, or whether they intend to provide different treatment approaches (psychotherapy vs. pharmacologic treatment).

The presence of a high degree of comorbidity between heterotypic clinical disorders collides with the main goal of the classification of mental disorders. This goal is to provide a common language or "frame of reference". A reliable diagnostic system should increase agreement, facilitate communication between physicians and with the users of mental services (C2R17). Additionally, it contradicts the theoretical basis of the DSM classification of mental disorders. The DSM is a categorical system that assumes that categorical diagnoses reflected underlying discrete and diverse disease entities (C2R14, 17, 22).

C02.S19. Prevalence of Comorbidity between Mental Disorders: Introduction

Early epidemiologic surveys in treatment-based samples have shown a widespread comorbidity between mental disorders. Ross et al. reported (C2R23) that in a sample of treatment-seeking patients suffering from alcohol dependence, 78% met criteria for a lifetime comorbidity for other mental disorder. Wolf et al. (C2R24) reported that half of the patients admitted to psychiatric unit in a major academic center, received more than one psychiatric diagnosis. They also reported a high correlation between substance abuse disorders and antisocial personality disorder, while affective disorders were highly correlated with each other in this population.

C02.S20. Comorbidity in Community Epidemiologic Surveys

With the advent of the large-scale psychiatric epidemiologic surveys, it was possible to have a more accurate estimate of the prevalence of mental and addictive disorders and their

respective comorbidity. The advantage of using population-based surveys and structured interviews reduced the bias from the results of previous treatment-based samples.

C02.S21. Comorbidity in the Epidemiologic Catchment Area Program

The Epidemiologic Catchment Area Program (ECA) (C2R25, 26, 27, 28) investigators reported that about 32% of adults in the US met criteria for one or more psychiatric or substance abuse disorder in their lifetime. In addition, comorbidity was widespread among most of the measured mental disorders included in the survey. When exclusion rules that prevented giving a second diagnosis were lifted, the authors reported that 18% of the total population had had at least two psychiatric disorders in their lifetime: namely, that 60% of those with at least one disorder, had at least one additional disorder. Investigators reported that somatization had the highest rate of comorbidity (100%), followed by antisocial personality, panic and schizophrenia (all with comorbidity rates over 90%).

C02.S22. Comorbidity in the National Comorbidity Study

The National Comorbidity Study (NCS) (C2R29), conducted a decade later than the ECA, showed similar results in a national based sample. The lifetime prevalence for any psychiatric or substance abuse disorder for adults was 48%. Stratifying the subjects by the number of lifetime prevalence diagnoses received, 52.0% of the sample met no criteria for lifetime disorder, 21.0% met criteria for only 1 disorder, 13.0% of the sample met criteria for only two disorders, and the remaining 14.0% of the sample met criteria for three or more disorders in their lifetime. When examining the total number of diagnoses by subject, 20.6% of the disorders were diagnosed in subjects that met criteria for only one psychiatric disorder, 25.5% of the disorders originated in subjects that were diagnosed with two psychiatric disorders, and, finally

53.9% of the lifetime disorders diagnosed in a sample were diagnosed in subjects that met criteria for three or more lifetime disorders.

In summary, the results of the NCS pointed out that comorbidity amongst mental disorders should be considered the norm more than the exception, as 56.25% of all the subjects that received a DSM diagnoses met criteria for more than one disorder. Notably, 79.4% of the lifetime diagnoses of psychiatric and substance abuse disorders diagnosed in the NCS sample were comorbid conditions (C2R29).

These findings from the NCS are remarkable, as they clearly highlight that the vast majority of the psychopathology found in the community is comorbid, and that a single psychiatric diagnosis is the exception to the rule.

C02.S23. Comorbidity and Debate about Classification

Considerable debate grew in the psychiatric literature about the concept of comorbidity and its implications for the classification of psychiatric disorders (C2R30). Some authors posited against the use of the concept of comorbidity in psychiatry (C2R31). Maj's main argument was that some psychiatric disorders did not meet the criteria of "disease or condition" that the Feinstein definition of comorbidity required. Maj posited that some anxiety and "neurotic" conditions were more dimensional in nature as they lacked a clear definition with each other and with normality.

Robert Spitzer (C2R32), and Lee Robins (C2R33) clearly supported the use of the concept of comorbidity in the classification. Spitzer saw no reason to abandon the use of the term comorbidity in psychopathology, while admitting that some measured comorbidity was artefactual (C2R32).

C02.S24. Research Domain Criteria and DSM-5

In view of the challenges to the current diagnostic classification, the National Institute of Mental Health launched the Research Domain Criteria (RDoC) project to create a new research framework to be implemented in pathophysiology (C2R34, 35). The RDoC project is intended to be a "next step", as it intends to shift the classification from the current clinically based system proposed by the third edition of the DSM to a new classification based on pathophysiology. The overarching goal of the RDoC project is to incorporate the findings of genomics and neuroscience into the classification of psychiatric disorders with the goal to identify new targets for treatment development, detect subgroups for treatment selection, and provide a foundation for future research findings. Thus, the RDoC is based on a cross-diagnostic or "tans-diagnostic" approach to overcome the challenges to validity of the categorical system posed by comorbidity. (C2R34, 35).

White the RDoC project is still underway, the fifth edition of the DSM was launched in 2013 (C2R36). During the process of drafting the DSM-5, widespread debate existed on whether the new classification of mental disorders should abandon the categorical model and substitute it for a dimensional perspective (C2R37). Despite the debate and the inclusion of dimensional instruments, the DSM-5 was still based on a categorical disorder model.

C02.S25. Comorbidity of Depression and Anxiety: Introduction

Depressive and anxiety disorders are amongst the most prevalent group of mental illnesses. The NCS investigators reported a lifetime prevalence of Major Depressive Disorder of 17.1% and of Dysthymia of 6.4% for adult men and women. The lifetime prevalence estimate for any anxiety disorder was of 25.9% for adults of both sexes. (Discriminated by condition: Panic

Disorder: 3.5%, Agoraphobia without Panic Disorder: 5.3%, Social Phobia: 13.3%, Simple Phobia: 11.3%, Generalized Anxiety Disorder: 5.1%) (C2R29).

C02.S26. Clinical Implications of the Comorbidity between Anxiety and Depression

A high rate of comorbidity between anxiety and depressive disorders can have a particular significance, not only due to the possible strength of the comorbid association, but also due to the high prevalence of these two conditions. In addition, anxiety and depressive disorders are usually treated by general practitioners in non-mental health settings. These practitioners are not extensively trained to understand the complexities and caveats of the diagnosis and the management of mental disorders. One set of symptoms could be ignored over the other, and patients might not receive an appropriate treatment that could address their condition. A busy clinician in a general medical clinic might not feel the need or have the expertise to inquire about possible comorbid symptoms of anxiety once the diagnosis of depression is given. Thus, comorbidity is not only a theoretical challenge for those interested in psychiatric diagnosis, but is also a practical issue, as the lack of appropriate diagnosis is often followed by inappropriate treatment.

C02.S27. NCS Findings on Comorbidity in MDD

Studies of diagnostic patterns in community samples have shown that mood disorders are widely comorbid with other psychiatric conditions, including anxiety disorders. NCS respondents had a 17.1% a lifetime prevalence of Major Depressive Disorder (MDD). Only 26% of the subjects with MDD had this condition as sole or "pure" disorder. This meant that 74% of all NCS respondents with a lifetime history of MDD had an additional disorder (C2R29). Kessler et al. (C2R29), further divided this group into two. The first subgroup, that included 14% of MDD

cases, was categorized as primary MDD, in which MDD preceded the comorbid condition, and the second subgroup, that included the extant 61.8% of total MDD cases, in which the condition could be considered "secondary". In this secondary group, the respondents had at least one of the other DSM disorders assessed in the NCS before or in the same year as their first onset of depression.

Of these 74% of the NCS respondents with lifetime MDD that had more than lifetime diagnoses condition, 24.7% met criteria for only one additional psychiatric disorder in their lifetime, 17.4% met criteria for only two additional conditions, and, finally, 31.9% met criteria for three or more additional mental disorders in their lifetime (C2R38, 39).

C02.S28.Prevalence of the Comorbidity between Anxiety and Depression

Focusing on the comorbidity between Major Depressive Disorder and all anxiety disorders, 58.0% of NCS respondents that met criteria for MDD in their lifetime, also met criteria for at least one anxiety disorder: namely, the NCS respondents diagnosed with MDD had 4 times the risk of meeting criteria for one anxiety disorder in their lifetime as compared to the total sample (OR= 4.2 (95% CI= 3.4 - 5.2)) (C2R38, 39).

C02.S29.Findings of the National Comorbidity Survey on Anxiety Disorders

The NCS findings for the comorbidity between Major Depressive Disorder and the anxiety disorders were as follows (percentage MDD respondents with the specified anxiety condition, odds ratio (OR) for the comorbidity between MDD and the specified anxiety disorder with 95% Confidence Interval). Generalized Anxiety Disorder: 17.2%, OR: 6.0 (95% CI:4.2, 8.6), Agoraphobia: 16.3%, OR: 3.4 (95% CI: 2.5, 4.6), Simple Phobia: 24.3%, OR: 3.1 (95% CI: 2.5, 3.8), Social Phobia: 27.1%, OR: 2.9 (95% CI: 2.3, 3.6), Panic Disorder: 9.9%, OR: 4.0 (95% CI:

2.7, 6.1), Posttraumatic Stress Disorder: 19.5%, OR: 4.0 (95% CI: 3.1, 5.2), respectively (C2R38, 39).

C02.S30.Findings of the National Comorbidity Survey Replication

The National Comorbidity Survey Replication (NCS-R) (C2R40) is a nationally representative face-to-face household survey of 9090 noninstitutionalized respondents aged 18 years or older. It was conducted between February 2001 and December 2002. Prevalence and correlates of MDD were obtained using the World Health Organization's (WHO) Interview (CIDI) (C2R41). The lifetime prevalence estimate for MDD was 16.2% for adult men and women. The majority of respondents (72.1%) with lifetime MDD reported at least one other lifetime DSM-IV disorder. Of the respondents with lifetime MDD, 59.2% also met criteria for lifetime anxiety disorder, 24.0% met criteria for a substance use disorder, and 30.0% met criteria for an impulse control disorder (C2R40).

When MDD is found in a comorbidity pair with any other mental disorder, MDD was considered the primary condition in only 12.35 % of the respondents. Of those respondents that met criteria for both MDD and an anxiety disorder, only 13.7% had MDD as the primary disorder. Of the respondents that met criteria for both MDD and a substance abuse disorder, 41.3% had MDD as the primary mental disorder. Finally, of the respondents that met criteria for both MDD and an impulse control disorder, 20.8% had MDD as the primary disorder (C2R40).

In the summary, the NCS-R findings confirm that MDD seems to be a highly comorbid condition, and appears later in the subject's life. Over half of the respondents that met criteria for depression, also met lifetime criteria for an anxiety condition. Anxiety disorders appear earlier in time in the vast majority of cases (87.3%).

C02.S31. Risk of Developing Depression with Primary Anxiety Diagnosis

The NCS investigators estimated the effect of the anxiety disorders in predicting a subsequent onset of lifetime MDD by using survival models in a sample of 1,769 adolescents and young adults who participated in the National Comorbidity Survey (C2R42). The survival coefficients were exponentiated to yield odd ratios (OR). For Any Anxiety Disorder, the OR to develop a subsequent MDD was 3.4 (95%CI: 2.8, 4.2). The results suggest that those who suffered from a previous anxiety disorder were 3.4 times more likely to develop a Major Depressive Disorder than the rest of the sample. Discriminated by disorder (OR (95% CI)); Panic Disorder: 3.3 (1.7, 6.3), Generalized Anxiety Disorder: 5.1 (2.8, 9.3), Posttraumatic stress Disorder: 2.8 (2.1, 3.8), Simple Phobia: 3.1 (2.4, 4.0), Social Phobia: 2.9 (2.2, 3.7), and, Agoraphobia: 2.7 (1.7, 4.2). Results were significant for all anxiety Disorders ($p < 0.05$) (C2R40).

C02.S32. Comorbidity from the Anxiety Disorders Perspective

Kaufman and Charney (C2R43) pooled data from several epidemiological and treatment samples to analyze the comorbidity of some selected anxiety disorders with other non-anxiety mental disorders, as well as the comorbidity between the individual anxiety disorders

For Panic Disorder, the authors reported a prevalence in the sample of 1.4%-2.9% of cases. Panic Disorder was found to be comorbid with any psychiatric disorder: 74%-90% of cases, with MDD: 56%-73%, with any other anxiety disorder: 10% of cases (C2R43).

For Social Phobia, the authors reported a prevalence in the sample of 1.4%-3.8% of cases. Social Phobia was found to be comorbid with any psychiatric disorder: 67%-92% of cases, with MDD: 15%-21%, with any other anxiety disorder: 27% of cases (C2R43).

For Generalized Anxiety Disorder (GAD), the authors reported a prevalence in the sample of 1.9%-6.6% of cases. GAD was found to be comorbid with any psychiatric disorder: 80-90% of cases, with MDD: 62%-67%, with any other anxiety disorder: 17% of cases (C2R43).

For Post-traumatic Stress Disorder (PTSD), the authors reported a prevalence in the sample of 1%-13.8% of cases. PTSD was found to be comorbid with any psychiatric disorder: 73-83% of cases, with MDD: 37%-48%, with any other anxiety disorder: 20% of cases (C2R43).

C02.S33. Longitudinal Course of the Comorbidity between Depression and Anxiety disorders

Coryell at al. (C2R44) reported that patients who suffered from MDD comorbid with panic attacks had more severe depressive symptoms and were less likely to recover in a 2 year follow up period when compared to individuals who suffered from MDD without panic attacks (C2R44).

Roy-Byrne et al. (C2R45) posited that, in the participants of the National Comorbidity Survey (NCS), there was a strong association between panic disorder and depression. Patients with this comorbidity had more severe symptoms, and increase need for clinical treatment as compared to those without comorbid depression and panic. The authors also reported that there was an increase in functional impairment, a higher number of lost work days, and a higher number of episodes of depression or panic in those individuals affected with this comorbidity (C2R45).

Based on findings from the Zurich Cohort Study, a prospective community study that has followed subjects with depression and anxiety over two decades, Merikangas et al. (C2R46) reported a high stability of depression and anxiety symptoms over time. Previous anxiety was a strong predictor of a subsequent onset of depression. The presence of both depressive and anxiety disorders was linked to poor treatment response and chronicity of the disease. The

authors challenged the idea that comorbid depression and anxiety should be considered as two different conditions based on their findings (C2R46).

C02.S34. Comorbidity and Response to Treatment

*Fava et al. (C2R47) reported findings from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) project. The STAR*D aimed to determine the effectiveness of several treatments for outpatients with nonpsychotic major depressive disorder. The authors compared the effectiveness of antidepressant therapy (citalopram) in 1,530 subjects with anxious depression (depression comorbid with anxiety symptoms) with the effectiveness of citalopram in treating 1,346 subjects suffering from non-anxious depression (depression without comorbid anxiety symptoms). The results of the STAR*D clearly indicated that anxious depression subjects had significantly lower rates of remission and needed longer follow-up time to achieve remission than the non-anxious depression subjects. In addition, subjects with anxious depression had more frequent and severe side effects than the patients with non-anxious depression. Lastly, subjects with anxious depression fared significantly worse than the subjects with non-anxious depression, when they were given an alternative or an additional antidepressant agent to address their symptoms (C2R47).*

C02.S35. Conclusion

In summary, comorbidity is a recent concept in medical literature that addresses a common occurrence that was overlooked in the past. The increase in the interest in the area stems from the realization that the majority of individuals are affected by more than one disease or condition at the same time.

In the general medicine field, the study of comorbidity is linked to the challenges that patients with multiple conditions can present in their diagnosis and clinical management. Another important challenge is the cost that the health services endure from the treatment of patients with multiple and severe conditions. In addition, there are no assurances that these enormous and increasing costs will translate into the improvement of health outcomes in this vulnerable population

In psychiatry, comorbidity has taken a different direction than the one described in general medicine. This difference is mostly due to our difficulties in accurately classifying mental disorders. The reliance on a categorical classification that provides coverage for a wide number of heterogeneous conditions, as well as the removal of hierarchies or barriers that could obstruct the practice of multiple diagnoses were also instrumental to the generation of comorbidity in the classification of mental disorders. The creation of the multiaxial diagnostic system also stimulated the adjudication of multiple diagnoses in the psychiatric patients.

While some comorbidities in psychiatry are expected as the natural consequence of our diagnostic schemes, others challenge the very validity of the classification system, as they provide clear evidence of the flaws in the premises of our classification system. Anxiety and depression are not two taxa or families of mental disorders that are categorically dissimilar. The evidence gathered from different large-scale, population based studies, shows that they anxiety and depression are intimately related, and they share a longitudinal "natural" course in the vast majority of cases.

The study of the relationship between the diagnoses of depression and anxiety in a population base sample, and the examination of its association with genetic markers appears to be a worthy task. We believe that this could shed some light into this complex issue and may assist into the development of future diagnostic improvements.

CHAPTER 03: LITERATURE REVIEW OF THE SEROTONIN TRANSPORTER GENE POLYMORPHISM AND ITS ASSOCATION WITH PSYCHOPATHOLOGY

C03.S01. Serotonin. Historical Introduction and Function

Serotonin (5-hydroxytryptamine, 5-HT), is a monoamine neurotransmitter that regulates several key physiological processes. First isolated by Rapport et al., serotonin received its name as a result of its vaso-constricting activity (C3R01). At the same time, serotonin was being studied in the digestive system, where it was found to play a key role in the intestinal motility and in the digestive process. (C3R02).

It was later discovered that serotonin was also present in the central nervous system (C3R03-4). Serotonin-producing neurons are localized in cell clusters centrally located, surrounding the reticular formation. Due to their central location they receive the name raphe nuclei. The dorsal raphe, the largest brain stem serotonin nucleus, contains approximately 50% of the total serotonin neurons in the mammalian CNS. From the raphe nuclei, serotonergic neurons project widely throughout the CNS, including the nigrostriatal and limbic systems and cortex (C3R05) where they play a regulatory function. Serotonin modulates noradrenergic and dopaminergic release in hippocampus and prefrontal cortex. The serotoninergic system can reduce or increase anxiety and impulsivity, either directly or by altering functions of other neurotransmitter systems (C3R06). In addition, serotonin modulates arousal and prevents uncontrolled anxiety or panic through its effect on the locus coeruleus, (C3R07).

Early psychopharmacologic studies evidenced that the monoamine neurotransmitters play a role in the development of depression. These investigations led to the catecholamine theory of depression. This theory postulates that a depletion of catecholamines, particularly norepinephrine, in brain synapses plays an etiologic role in the development of depression

(C3R08). Pharmacologic studies revealed that antidepressant agents also interacted with the serotoninergic system. Thus, investigators postulated a role for serotonin similar to the one of the catecholamines: namely, that at a deficiency in serotoninergic neuronal function was at the core of the pathophysiology of some depressive states (C3R09-11).

C03.S02. The Serotonin Transporter (SERT)

The serotonin pathways configure a highly complex system, regulated by 14 different receptors and transporter sites (C3R06). Presynaptic receptors are auto-receptors that decrease activity of serotonergic neurons and have mostly anxiolytic effects, while postsynaptic receptors cause anxiety-like behaviors in animals (C3R12).

The serotonin transporter (SERT) is a pre-synaptic plasma membrane transporter. It belongs to the subclass SL6 gene family of the sodium/chloride- coupled transporters that also includes transporters for the monoamines norepinephrine and dopamine, as well as for the neurotransmitter GABA (gamma-aminobutyric acid) and the amino acid glycine. The SERT plays a key role in the modulation of the serotonergic neurotransmission. It regulates the magnitude and duration of serotonergic responses, by capturing the 5-HT from the synaptic cleft. The SERT has been an important focus of research, as it has been established that both the tricyclic antidepressants (TCAs) as well as the newest serotonin reuptake inhibitors (SRIs) exert their initial pharmacological effect by binding to the SERT. The blockade of the SERT function increases the levels of serotonin in the synaptic cleft. This increase in serotonin promotes secondary changes in the serotoninergic transmission both at the presynaptic and postsynaptic levels that are posited as the mechanism of action for both the TCAs and SRIs (C3R05, C3R13).

C03.S03. The Serotonin Transporter Gene Polymorphism

The human serotonin transporter (SERT) is encoded by a single gene (SLC6A4) located on the long arm of chromosome 17 (17q111-17q12). The SLC6A4 gene is organized into 14 exons spanning approximately 31kb. The most investigated area of the SLC6A4 is the serotonin transporter gene promoter region (5-HTTLPR), located 1kb upstream of the SERT gene transcription initiation site. The 5-HTTLPR has been the object of great attention due to a functional polymorphism. This polymorphism is constituted by a 44 base pair deletion /insertion in the 5' regulatory region. The polymorphic variant that includes this 44 base pair is referred as the long (L) allele, the variant without the 44 base pair is called the short (S) allele (C3R14, C3R15). Lesch et al. reported that the 5-HTTLPR genotypes were distributed according to Hardy-Weinberg equilibrium: 32% l/l, 49% l/s, and 19% s/s (C3R15).

The short (S) variant of the 5-HTTLPR was associated with lower levels of gene transcription (C3R16, C3R17). This decreased level of transcriptional efficacy of the SERT by the short (S) allele has been associated with several psychiatric disorders. The primary focus of several studies has been the link of the short (s) allele to major depression, and suicidal behavior (C3R18, C3R20).

C03.S04. Beyond Bi-Allelic SERT Polymorphism

Hu et al. reported an additional single nucleotide polymorphism in the long allele. This site, identified as rs25531, has two variants one with adenine designated as LA, and the second one with guanine, designated as LG (C3R21-23). The LG allele has been associated with a reduced gene transcription of SERT mRNA and protein compared to the LA allele (C3R24-25).

Nakamura M et al. (C3R26) identified ten novel sequence variants for the 5-HTTLPR. The authors concluded that the alleles that were originally reported as S and L could be divided

into four and six kinds of allelic variant, respectively. The investigators also reported a significant ethnic difference between Japanese and Caucasian populations in the distributions of alleles and genotypes

C03.S05. The Variable Number of Tandem Repeat (VNTR) Polymorphism in Intron 2

A variable number of tandem repeat (VNTR) in intron 2 (STin2 VNTR) is the third polymorphism that was described in the SLC6A4 gene. It consists of a variable number (9, 10, or 12) of nearly identical 16/17bp segments. The 10-repeat and 12-repeat alleles of a 16/17 bp are present in all ethnicities, and the rare 9-repeat allele appears only in people of European or African descent (C3R55-56). The 9-repeat allele (STin2.9) has been associated with an increased risk for major depression and bipolar disorder (C3R57-58). The 12-repeat allele (STin2.12) has been associated with bipolar disorder and schizophrenia (C3R59-61).

C03.S06.Association of 5-HTLLPR with Psychiatric Disorders and Antidepressant Response

The potential association of the SERT gene polymorphism with clinical psychiatric disorders and antidepressant response has been the target of multiple investigations. A full review of the whole literature in the area is beyond the scope of this review. The main areas of this research have been the association of 5-HTLLPR with: 1) depression (both primary and in response to stressful events), 2) suicidal behavior, 3) non-affective mental disorders, and 4) response to antidepressant treatment.

C03.S07. Association of 5-HTLLPR with Depression

Several studies examined the association of 5-HTTLPR with Depression. Findings have been so far, contradictory. Lesch et al. (C3R15) were the first in reporting the association between S allele (S/S or S/L) and a neuroticism factor (anxiety and depressive symptoms and traits). Caspi et al. (C3R26) reported that individuals who were carriers and homozygous for the S allele exhibited more depressive symptoms, diagnosable depression, and suicidality in relation to stressful life events than individuals homozygous for the long allele This was considered an influential study that postulated a gene-by-environment interaction role for the SERT, in which an individual's response to environmental insults is moderated by the 5-HTTLPR. The association between SERT polymorphism and an increase risk of depression in an interaction with stressful life events was challenged by a meta-analysis conducted by Risch et al. (C2R66), only to be later confirmed by a more recent meta-analysis conducted by Karg et al. (C2R67).

Eaton et al. (C3R28) reported that individuals from the Epidemiologic Catchment Area Follow-Up Study (C3R29) who were heterozygous and homozygous of the S allele had a higher risk of an initial episode of depression, and, paradoxically experienced episodes of shorter duration as compared to non-carriers. This study is particularly relevant as it examines the incidence of depression and its association with the 5-HTLPLPR in a population based sample.

Several studies (C3R30-37) confirmed the association of 5-HTTPLR with depression, while others failed to find any significant association (C3R38-40). In a recent collaborative meta-analysis, Cluverhouse et al. (C3R41) examined the association between the allele of the 5-HTTLPR serotonin transporter promoter region and the increased risk of depression in individuals exposed to stressful situations. This massive undertaking involved the collaboration of multiple researchers in multiple academic centers. The analysis included 31 datasets containing 38 802 European-ancestry subjects. The investigators were unable to find a significant interaction of the S allele of 5-HTLLPR and depression due to stressful situations

C03.S08. Association of 5-HTLLPR with Depression with Suicidal Behavior

The evidence regarding the association between the 5-HTTLPR polymorphism and suicidal behavior is conflicting. While three separate meta-analyses done by Anguelova et al. (C3R42), Lin et al. (C3R43), and by Li et al. (C3R44) reported a positive association of the S allele and suicidal behavior, several studies (C3R45-47) contradict these findings, reporting negative findings

C03.S09. Association of 5-HTLLPR with Antidepressant Response

The SERT is one of the main modulators of serotonin transmission, and the primary site of action for several antidepressant agents, especially the serotonin reuptake inhibitors (SRIs). Several reports have demonstrated that the L/L allele polymorphism in 5-HTTLPR is associated with an increased effectiveness in antidepressant response. Yu et al. (C3R48) reported that patients with the L/L genotype had a significantly better response to fluoxetine (20-60 mg/day) than the S/S carriers. Zanardi et al. (C3R49), as well as Smeraldi et al. (C3R50) posited that L allele carriers (S/L and L/L) had a better response to fluvoxamine when compared to S homozygous.

C03.S10. Association of 5-HTLLPR with Non-Affective Mental Disorders

In addition to the literature linking the SERT polymorphism to the affective disorders, several studies have reported its association with several non-affective mental disorders. Calati et al. (C3R51) reported an increased risk for eating disorders, in particular Anorexia Nervosa in S carriers. Lee et al. (C3R52) reported that subjects diagnosed with Posttraumatic Stress

Disorders had a higher frequency of the low expression (s/s) genotype than normal controls. These results were contradicted by Grabe et al. (C3R53), who reported a strong additive gene-environment interaction with the high expression L(A) allele of 5-HTTLPR and frequent trauma in PTSD

A meta-analysis conducted by Feinn et al. (C3R62) reported that the S allele was significantly associated with Alcohol Dependence, as well as with an increased risk to suffer from a comorbid psychiatric condition, an early-onset or a more severe subtype of Alcohol Dependence.

C03.S11. Association of 5-HTLLPR with Obsessive Compulsive Disorder (OCD)

The SERT gene promoter region polymorphism has been associated with OCD in case controls and family based studies. In a case control study that included 75 cases of Caucasian OCD patients, Bengel et al. reported that the OCD subjects were more likely to carry two copies of the long SERT long (l) allele as compared to the 397 matching controls (C363). Bloch at al reported a significant association between the (l) allele and OCD in children and Caucasians (C3R54)

C03.S12. Association of 5-HTLLPR with Panic Disorder

The association between the SERT gene promoter region and Panic Disorder has been investigated with mixed results. Lesch et al. reported that in a sample of 505 individuals, the SERT gene promoter polymorphism accounted for 3 to 4 % of the total variation and 7 to 9 % of the inherited variance for anxiety-related personality traits in individuals as well as sibships (C3R15). Heils at al. reported that the SERT gene promoter polymorphism accounted for 4 to

5% of the population variation in anxiety related behavioral traits (Cc3R24). Strug et al. reported no association of the SERT promoter gene polymorphism with an increased risk for Panic Disorder in a sample of N=179 subjects sampled from the NIMH Human Genetic Initiative (C3R64). In addition, Blaya et al. reported no association of the SERT promoter gene polymorphism in a case-control candidate gene association study with 107 patients with Panic Disorder (C3R65)

C03.S13. Summary and Conclusions

There is a vast body of literature on the potential association of the 5-HTTLPR with an extensive list of psychiatric conditions. The results of these investigations have been, so far, inconclusive.

Considering the role of serotonin transmission in the central nervous system, and the role of the SERT in the regulation of serotonin transmission, the existence of a polymorphism in the gene that codes the SERT should continue to be an area of active interest in research. Especially if this polymorphism impacts on the SERT function, and therefore, on the serotonin transmission.

The aim of this investigation was to study the potential impact of the 5-HTTLPR in psychopathology. We explored the potential role of the 5-HTTLPR beyond its association with the prevalence of individual mental disorders. We examined the association of the 5-HTTLPR with the presence of an increase burden of comorbidity of mental disorders. This approach allowed us to measure of the overall vulnerability that the 5-HTTLPR can confer to the carrier subjects.

CHAPTER 04. PART 01.

METHODS: STUDY PARTICIPANTS SELECTION PROCESS

S04. P01.S01. Introduction to Participant Selection

The sample population for this study was the result of a three-phase selection process. The first phase involved the development of the original cohort for the Baltimore site of the Epidemiologic Catchment Area in the early 1980's (C4R01). The second phase consisted in a series of waves that, during the 1990's, re-sampled the cohort obtained in the first phase. These waves are generically called the Baltimore Epidemiologic Catchment Area Follow-up (EFU) (C4R02- C4R04). The third phase entailed the development of a sub-sample of the EFU for this investigation, the Comorbidity and Serotonin Transporter Gene (C4R06- C4R07). (Figure C4AF01)

S04. P01.S02. First Phase: The Epidemiologic Catchment Area Program (ECA)

The Epidemiologic Catchment Area Program (ECA) was a collaborative research project designed to assess the prevalence of mental and addictive disorders and to estimate the use made of different sectors of the mental health system. It was designed by the National Institute of Mental Health (NIMH) and five research groups in five different cities in the US. These included Yale University in New Haven, Connecticut; Johns Hopkins University in Baltimore, Maryland; Washington University in St Louis, Missouri; Duke University in Durham, North Carolina; and University of California in Los Angeles, California (C4R01).

The ECA was designed as a response to some of the major epidemiological and research gaps identified by the 1978 report of the President's Commission on Mental Health (C4R01). It represented the first coordinated multi-site, large scale, community based epidemiologic study in the area of mental disorders that was able to use advances in diagnostic

criteria, standardized diagnostic interviews and survey methods. (C4R01).

Over 20,000 subjects were examined in two series of interviews between 1980 and 1983 in the five sites in the US. Subjects were aged 18 and older living in regular households, as well as in nursing homes, prisons and institutions. Participants were selected by the five research groups. The groups used probabilistic sampling to select subjects who were representative of their respective catchment area. At the first encounter, respondents gave informed consent and permission to be interviewed again. Respondents at all sites were re-interviewed 12 months later (C4R01-04).

The target population for the Baltimore ECA site consisted of the household residents of East Baltimore (an area with 175,211 adult inhabitants in 1981). Out of the 4238 individuals that were probabilistically designated for interview, 3,481 subjects completed the interviews. This represented an 82% completion rate of the original 4,238 that were designated (C4R01-04).

S04. P01.S03.Diagnostic Interview Schedule Interview in the ECA

Subjects of the ECA were interviewed using the Diagnostic Interview Schedule (DIS) (C4R07). The DIS is a structured clinical interview that was developed for the ECA. The DIS was designed to provide a standardized and reliable psychiatric diagnosis while administered by lay interviewers as the large-scale dimension of the ECA study precluded the use of trained professionals as interviewers. (C4R07).

S04. P01.S04. Second Phase: Baltimore Epidemiologic Catchment Area Follow-Up Study

During the 1990's, the subjects of the original Baltimore ECA Study cohort were contacted and re-interviewed in successive waves in order to participate in the ECA Follow-up Study (EFU)

(C4R02-06). During the period of time between the ECA (1980-3) and the first wave of the EFU (1993-4), several subjects were lost to follow-up. Out of the 3,481 respondents of the original ECA, 848 people had died, 415 individuals could not be located, and 298 refused to participate. Ultimately, 1920 subjects of the original 3,481 Baltimore ECA participants (approximately 73% of the 2633 survivors), were re-interviewed for the EFU (C4R02). The first wave of EFU respondents did not differ from the non-respondents in terms of age, sex, and rates of depression and other psychiatric disorders (C4R02)

S04. P01.S05. Diagnostic Interview Schedule Interview in the EFU

Following the protocol of the original ECA, the subjects of the EFU were interviewed using the Diagnostic Interview Schedule (DIS) (C4R07). For the EFU, the DIS version III, revised was used. This version of the DIS provided diagnostic algorithms for DSM-III-R. DIS interviews were designed to be as similar as possible as to the ones conducted for the ECA. Interviews were done by lay interviewers in the respondents' household (C4R02-05).

S04.P01.S06. Third Phase: Comorbidity and Serotonin Transporter (SERT) Gene Polymorphism

The sample for this study, the Comorbidity and Serotonin Transporter (SERT) Gene Polymorphism, was obtained from the EFU cohort. The selection process intended to oversample subjects that had "filtered positive" (RE06), on the ECA or the EFU on selected DSM-IIIR psychiatric disorders in the DIS. The seven psychiatric disorders of interest were: Major Depressive Disorder, Panic Disorder, Agoraphobia, Social Phobia, Obsessive-Compulsive Disorder, Alcohol Use Disorders, and Cognitive Impairment. The sample for this phase also randomly selected subjects that had not endorsed the aforementioned disorders in neither of the two previous sampling phases (C4R05- 06).

S04. P01.S07. Schedule for Clinical Assessment in Neuropsychiatry Interview

Eligible subjects were invited to the Johns Hopkins Hospital for an interview with a psychiatrist. The subjects were invited to complete an assessment using the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (C4R08-09). The SCAN was administered by board-certified psychiatrists who had undergone a SCAN training course at an official World Health Organization SCAN training center. The findings of the DIS were concealed to the examining psychiatrists until the SCAN assessment was completed. After the interview was concluded, the psychiatrist dictated a 2- or 3-page summary for each subject in a standard format that described the subject's clinical picture, ensured inclusion of important idiosyncratic details, and explained possible disagreements with the DIS as well as overall diagnostic impressions and decisions that, in the view of the psychiatrist, were not clearly supported by the SCAN. The first 20 interviews of each rater were discussed in detail in a conference attended by the other interviewing psychiatrists. The rest of the interviews were discussed with at least one other interviewing psychiatrist. In the event of a challenging case, a full conference was scheduled to review the findings (C4R05-06).

For the Baltimore ECA follow-up, several items were added to the SCAN, version 1.0. Some of these additions were incorporated into the second edition of the SCAN. The following items were added in the section of depression: social withdrawal, increase in appetite, age at first onset of dysphoria or anhedonia, age at first onset of depressive delusions, organic cause of symptoms about thinking and concentration, and age at first onset of sleep problems (C4R06). A computer algorithm was written in order to achieve a DSM-III-R diagnosis. This algorithm was based on the World Health Organization SCAN algorithm previously written for the International Classification of Diseases, 10th Revision (C4R05-06).

The Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (C4R08-09) was developed with the encouragement and support of the Task Force on Psychiatric Assessment Instruments under the auspice of the World Health Organization. Its purpose was to improve

the accuracy and reliability of measurement and classification of psychiatric disorders. The core part of SCAN is the tenth version of the Present State Examination (PSE-10), a semi-structured interview (C4R08-09).

The interview is based on clinical "cross-examination" with the aim of discovering whether each of a comprehensive list of symptoms is present in the subject and, if so, with what degree of severity. This decision is made by the examiner, not by the respondent. For most symptoms, a form of questioning is suggested, although the interviewer is free to depart from this and from the order of questioning, if necessary, with the goal to obtain clarity (C4R08-09).

The Present State Examination had its origins in studies conducted in the late 1950s. Updated versions were used for large scale international studies as the United States-United Kingdom Diagnostic Project, and the International Pilot Study of Schizophrenia. It is important to note that, the PSE was originally not a "diagnostic" scale, but an instrument aimed at describing psychopathological phenomena comprehensively, precisely, and accurately (C4R08-09).

The PSE-10 is divided into two parts. Part I contains the sections concerned with neurotic symptoms, eating, and substance abuse disorders. The second part deals with psychotic experiences and affect, speech, and behavior. All these symptoms are rated during the examination. In the SCAN, the course of a clinical disorder, for purposes of classification, is either regarded as a single "primary" period or divided into two kinds of period, primary and secondary. If a single primary period is clinically appropriate (as decided by the examiner), it is fairly simple to accumulate the relevant database and apply the nosological algorithms. The primary period is further classified into three subtypes: 1) present state, 2) present episode, and 3) lifetime ever. (C4R08-09).

In summary, the SCAN enables the collection of symptoms, diagnoses (both current and past), as well as treatment history and socioeconomic information, in a way that is both comprehensive and reliable. It enables the clinician to construct a diagnosis from symptom level

data (bottom-up approach), instead of evaluating the presence or absence of pre-determined DSM diagnostic criteria (top-down approach). This feature of the SCAN allowed for the collection of symptom level and diagnostic information on a wide variety of symptoms and diagnoses on a population that was sampled probabilistically from the community.

S04. P01.S08. Genetic Sampling of Study Participants

Subjects provided a venous blood sample. In the event of refusing to provide a blood sample, a swab buccal mucosa swab was obtained. Blood samples collected were placed onto a specially formulated "Isocode" Card. DNA was isolated from peripheral blood leukocytes using Puregene Blood Kit chemistry on an Autopure LS automated DNA purification instrument (Qiagen, Valencia, Calif). Following manufacturer's protocols, blood collected on Isocode Cards was isolated by heating hole punches in distilled water at 95 degrees centigrade for 30min. Buccal cell swabs were manually isolated using Puregene DNA isolation kit (Qiagen). Manufacturer's protocols were used in this procedure. DNA concentrations were established by spectrophotometry using a DU 530 Life Science UV/Vis Spectrophotometer (Beckman Coulter, Brea, California). The serotonin transporter genotype was determined by polymerase chain reaction amplification (C4R10).

A total of 602 (74.1%) of the 847 participants provided a DNA sample and were genotyped for SERT. The 219 non-genotyped subjects had similar distributions of gender, race, and educational level (Table C4AT01). The genotyped sample was slightly younger than the non-genotyped sample. Mean age of genotyped sample was 47.19 years old (95% CI: 46.18; 48.20). Mean age of non-genotyped sample was 51.37 years old (95%CI 49.23; 53.52) (Table C4AT01).

The frequencies of SERT polymorphism in the sample was: "l/l", 280 (44.6%); "l/s", 274 (43.6%); and "s/s", 74 (11.8%). The distribution of the alleles followed the Hardy-Weinberg Equilibrium Chi2 (1df): 0.38 (p>0.5). For the analysis, we combined the "s/s" and "l/s" alleles into a carrier group and compared these groups to the non-carrier group that only included those with "l/l" genotype (Table C4AT02). This was done following previous literature that had analyzed the functional effect of the "s" or short carrier allele in both in vitro and in vivo (C4R10-11).

CHAPTER 04. PART 02. ANALYTICAL APPROACH

C04.P02. S01. Introduction

In this section, we will detail the analytical approaches used in the study. Similar information is included in each individual chapter. We will list the different aims of each chapter, followed by the analytical approaches used

C04. P02. S02. Analytical Approach for Chapter 04. Aim 01: Missing Genetic Information for Covariates

We used univariate Statistics (Chi Square Tests and Fischer's Exact Test for count data, Student's T-Test for and Wilcoxon rank-sum test for continuous data) to determine whether the study participants who provided no sample for genetic testing (non-genotyped sample) were significantly different from the subjects who have a sample for genetic testing (genotyped). We tested the differences with the following variables that could be a potential confounder. These variables included: 1) Age in years, 2) Gender, 3) Race (Dichotomized as Whites vs Non-Whites), 4) Educational Level (Dichotomous: High School Diploma, No High School Diploma), 5) Educational Level (Categorical: High School Incomplete, HS Complete, College Incomplete, College Complete), 6) Marital Status (Dichotomous: Married versus ingle/ Divorced/ Separated/ Widowed)

C04. P02. S03. Chapter 04 Aim 03: Distribution of SERT Polymorphism

We determined the frequency distribution of Serotonin Transporter Gene (SERT) short "s" allele in the sample. We examined whether the allele frequency follows the Hardy-Weinberg Equilibrium.

C04. P02. S04. Analytical Approach for Chapter 05. Aim 01. Determine the Lifetime Prevalence of the Selected Mental Disorders

Using Chi Square Tests and Poisson Regression Analyses, we calculated the lifetime prevalence (LP) of selected psychiatric disorders with their corresponding 95% Confidence Interval (95%CI)

C04. P02. S05. Chapter 05 Aim 02. Determine the Association of the Individual Mental Disorders with the SERT (S) Polymorphism

Using Chi Square Tests and Poisson Regression Analyses, we calculated the LP of the each mental disorder for the genotyped and non-genotyped sub-samples. Using Poisson Regression, we later calculated a Prevalence Rate Ratio for each disorder with their corresponding 95% Confidence Interval (95%CI). These Prevalence Ratios measured the association of the SERT status with the risk for LP for each condition.

C04. P02. S06. Chapter 05 Aim 03. Determine the Comorbidity of the Individual Mental Disorders for the Whole Sample (Genotyped+ Non-Genotyped; n= 847)

We first explored the patterns of comorbidity between the individual mental disorders for the whole sample using tetrachoric correlations. Using Logistic Regression Analysis, we

calculated the Odds Ratios for each comorbid pair. This yielded an estimate of the strength of the association between the all pair of conditions included in the study sample

C04. P02. S07. Chapter 05 Aim 04. Determine the Association of the SERT (s) Allele with Comorbidity of the Individual Mental Disorders

We first explored the patterns of comorbidity between the individual mental disorders for the SERT (s) allele carrier and the non-carrier subgroups using tetrachoric correlations. Using Logistic Regression Analysis stratified by the patients affected by the first selected condition, we calculated the odds of comorbidity for the carriers and non-carriers. Thus, for those affected with a given condition, we obtained an odds ratio that measured the odds of comorbidity of the carriers to be diagnosed with a selected second condition divided by the odds of the non-carriers to be diagnosed with the same second condition. Using this approach, we were able to determine whether the SERT (s) allele carrier status was associated with an increased risk for any given comorbidity between the selected conditions.

C04. P02. S08. Chapter 05 Aim 05. Determine the Distribution of Subjects with Multiple Diagnoses in the Sample

We used univariate statistics (Chi Square Test and Fischer's Exact Test) to determine the distribution of participants with multiple LP diagnoses in the sample. We examined the association of gender, and age in this distribution

C04. P02. S09. Chapter 05 Aim 06. 5. Determine the Association of the SERT (s) Allele Carrier State with the Number of Lifetime Prevalence Diagnoses

We used Chi Square and Fisher's Exact Test to we examine the association of the SERT (s) allele carrier status with distribution of affected subjects.

We subsequently grouped the subjects into dichotomous categories according to the number of lifetime diagnoses received in order to perform a logistic regression analysis that could allow us to adjust for possible confounding variables. In the first analysis, we divided the sample into a first group that included the subjects with one or more diagnoses, and a second group that included the subjects with no diagnoses. For the second analysis, we divided the subjects into a first group that included the subjects who had received two or more diagnoses, and a second group that included the subjects who had received one or no diagnoses. We performed a Logistic Regression Analysis to determine the risk for the SERT (s) carrier subjects to belong to the category that presented with the higher number of diagnoses as compared to the risk for the non-carrier subjects. We adjusted the regression models for the effect of gender, age, marital status, and ethnicity.

C04. P02. S10. Analytical Approach for Chapter 06: Comorbidity: Methodological Approaches

In this section, we evaluated the comorbidity burden in the sample using different and complementary analytical approaches.

In the first approach, we examined the ratio between the number of comorbidities and the number of diagnoses in each individual mental disorder, as in the sample as a whole.

In the second approach, we examined the importance or impact of each comorbidity pair or dyad. We examined this impact using three different vantage points or perspectives. In the first perspective, we analyzed the importance of each comorbidity dyad as measured by their overall sample prevalence. In the second vantage point, we analyzed the impact or weight of all comorbidity pairs to each of their integrating or member mental disorders. In the third vantage

point, we obtained a measure of the strength of each comorbidity pair with respect to both of its integrating mental disorders.

Lastly, in the third approach, we examined the association between each individual disorder and the presence of individuals in the sample that received multiple diagnoses. For this last approach, we stratified the individuals in the sample according to the number of diagnoses received (0, 1, 2 or more conditions) and we then examined the association of the prevalence of the individual conditions in each diagnostic stratum with the number of affected individuals in each diagnostic stratum.

Chapter 06 includes detailed information on all the analytical approaches used for the analysis of the burden of comorbidity in the study sample. A mathematical appendix that provides further background is also included.

C04. P02. S11. Analytical Approach for Chapter 07. Part 1. Aim 01; Examine the Time to Diagnoses for Selected Disorders in the Whole Sample

We used the Kaplan-Meier (Product Limit) Approach. Subjects started to accrue exposure time at the moment of their birth. The follow-up time ended at the time the respondent had the "event" or "failure" of interest: namely, the reported age when they met criteria for the selected disorder. Subjects who never met criteria for the selected disorder at the moment of the study, were censored at the age of the interview. We used this technique for each selected disorder in which we had information of the age of onset in the sample. By calculating the quotient between the number of events (first time occurrence of the disorders) and the total person-years accrued by the subjects, we were able to obtain an Incidence Rate for each condition.

C04. P02. S12. Analytical Approach for Chapter 07. Part 1. Aim 02: Determine the Association of the SERT (s) allele carrier with the Time to Diagnoses for Selected Disorders

Using Kaplan-Meier Approach, we calculated the events and exposure time both for the carriers of the SERT (S) allele and for the non-carrier subjects. We obtained separate Incidence Rates for both groups in each condition included in the study. The ratio between the Incidence Rates of carriers and non-carries for each condition is a measure of the association of the carrier state with the onset of the examined mental disorder.

We later calculated Log-Rank tests for each condition to estimate whether the survival curves (in our case the time to diagnosis) were different between groups: namely, whether the carriers had a different time trajectory in attaining each diagnoses under examination

Finally, we performed a Cox Proportional Hazards Regression Analysis for each condition in the study. This approach enabled us to examine the association the SERT (s) allele carrier to the survival time (in our case, time to attain diagnosis). The Cox Proportional Hazard Regression model also allowed us to adjust the hazard estimates by potential confounding variables: namely, gender, ethnicity, and marital status. Thus, using this technique we were able to obtain a Hazard Ratio between the carrier and non-carrier participants for each condition examined, both unadjusted and adjusted for the aforementioned variables. Lastly, we examined whether our analysis for each condition met the proportional-hazards assumption required in the Cox Regression Model.

C04. P02. S13. Analytical Approach for Chapter 07. Part 02. Use of Psychotropic Agents and Its Association with the Serotonin Transporter Gene Polymorphism

Using Pearson's Chi-Square and Fisher Exact Tests, we explored the association of the carrier state for the Serotonin Transporter Gene (SERT) short (s) allele with the use of

antidepressant medications, anti-anxiety agents, hypnotic agents, antipsychotic agents, and, anti-manic agents at the moment of the interview. In addition, we created cumulative categories to improve the power of the analyses. We combined anti-anxiety and antidepressant agents into one category. Finally, we combined all psychotropic agents that were included in the interview into one category to explore if there was any association between the use of any individual psychotropic agent or the use of psychotropic agents as a class with the SERT (s) allele carrier status.

CHAPTER 05: LIFETIME PREVALENCE AND COMORBIDITY OF PSYCHIATRIC DISORDERS AND THEIR ASSOCIATION WITH SEROTONIN REUPTAKE CARRIER POLYMORPHISM

C05. S01. Lifetime Prevalence of Selected Disorders

We examined the lifetime prevalence (LP) of Alcohol Dependence, Alcohol Abuse, Opioid Dependence, Schizophrenia and other Psychotic Disorders, Major Depressive Disorders (MDD), Bipolar Disorder, Panic Disorder, Agoraphobia, Social Phobia, Obsessive Compulsive Disorder (OCD) , Generalized Anxiety Disorder (GAD), Simple Phobia, Dysthymic Disorder, Anxiety Disorder Not Otherwise Specified, Depressive Disorder Not Otherwise Specified, and Adjustment Disorder with Depressed Mood in the study population using Poisson regression models and Chi Square Tests. Table C5T01 summarizes the un-weighted LP prevalence estimates with 95% confidence intervals (CI) of the 16 Axis I disorders examined. Column 01 summarizes the estimates for the whole sample (N=847), column 02 for the genotyped sub-sample (N=628). The disorders with the highest prevalence were: Alcohol Dependence (20.90 (95% CI: 18.32; 23.82)), followed by Major Depressive Disorder (17.95 (95% CI: 15.54; 20.73), Simple Phobia (12.51 (95% CI: 10.47; 14.95)), and Social Phobia (11.81 (95% CI: 9.82; 14.91), respectively.

C05. S02 Association of Lifetime Prevalence estimates of the examined disorders with Serotonin Reuptake Transporter (SERT) Polymorphism

We examined the association of the lifetime prevalence of the 16 disorders included in this investigation and the SERT polymorphism using logistic regression models. In other words, we evaluated whether the carriers of the short (S) allele of the SERT polymorphism had an increased risk for receiving a lifetime diagnoses of the 16 disorders examined in this investigation

Table C5T01 summarizes in column 03 the LP estimates of each individual mental disorder in the serotonin transporter gene (S) allele (SERT) carrier sub-sample (N=348), and, column 04 summarizes the estimates in the SERT non-carrier sub-sample (N=280). Column 05 summarizes the LP estimates of SERT carriers divided by the LP estimates of the SERT non-carrier for each disorder. Column 06 summarizes significance estimates (p-values) for each of the ratios compiled in column 5. Panic Disorder was the only condition examined in the study sample that had a significant ratio (2.61 (95% CI: 1.20; 5.69), p=0.02). Thus, we can state the carriers of the (s) in this study sample have a risk of diagnosis with Panic Disorder in their lifetime that is 2.61 higher than those who are non-carries of the (s) allele. Lastly, we examined the association between the (s) carrier status and the LP estimates of the conditions examined in this study stratified by gender (Table C5T02). The association between the (s) carrier status was similar for both male (2.1) and female participants (2.79) affected by Panic Disorder. Due to difference in sample size for both genders, the ratio was only significant in women.

In addition, the (s) allele carrier vs non carrier ratio for Bipolar Disorder was 2.21 (Table C5T01). This translates into a risk for the (s) allele carriers to be diagnosed with Bipolar Disorder twice as high as the one of the non-carriers. Unfortunately, due to the sample size limitation, this latest finding was not statistically significant.

C05. S03. Summary and Conclusions. Lifetime Prevalence Estimates and their association with the (S) carrier allele

In our sample, the (s) carriers had a statistically significant higher risk of being diagnosed with Panic Disorder during their lifetime. This risk was 2.61 higher in those who were carries as compared to the non-carriers of the (s) allele. Carriers for the (s) allele had also twice the risk of developing Bipolar Disorder as compared to the non-carriers, but this finding was not statistically significant. Being a carrier of the (s) allele had no association with an increased risk of being diagnosed with any other of the examined mental disorders in our study sample. In various conditions, namely Agoraphobia, Obsessive Compulsive Disorder, and Dysthymic Disorder, the (s) carrier status appears to confer a protective effect (as evidenced by Rate Ratios as low as 0.64 in GAD) to develop these disorders, although the small number of affected individuals precluded from obtaining statistically significant results. No evidence was found that the (s) allele carrier status could have a gender-specific effect.

C05. S04. Comorbidity between the Lifetime Prevalence of the individual psychiatric disorders

Table C5T03 summarizes the significant tetrachoric correlations between all the 16 mental disorders for the whole study sample (N=847). Table C5T04 displays the comorbidity odds ratios between the individual mental disorders obtained from logistic regression models for the whole study sample.

We can posit that two patterns of correlations or comorbidities between the individual mental disorders emerge. Anxiety Disorders were highly comorbid with each other, and with the

mood disorders and alcohol dependence. In addition, mood disorders had a high degree of comorbidity with Alcohol Dependence.

Agoraphobia, Social Phobia, Obsessive Compulsive Disorder, Generalized Anxiety Disorder, and Simple Phobia had a strong correlation with each other and with mood disorders (MDD and Bipolar Disorder). As an example, Table C5T04 displays in row(r) 07, column(c) 07, the odds of having a lifetime prevalence diagnoses of Panic Disorder is 5.51 times higher in subjects that have a lifetime diagnoses of Social Phobia than in those who did not receive this diagnosis. In r08, c09, the odds of receiving a diagnosis of OCD during their lifetime was 7.96 times higher in subjects who have received a diagnosis of Social Phobia than in subjects who did not receive this diagnosis.

Major Depressive Disorder and Bipolar Disorder were highly comorbid with the majority of the anxiety disorders. The odds of receiving a diagnosis of GAD during their lifetime was 3.19 times higher in subjects who have MDD than in subjects without this diagnosis. Bipolar Disorder was highly comorbid most anxiety disorders: namely, with Panic Disorder (4.14), Agoraphobia (3.76), Social Phobia (2.46), OCD (4.76) and, GAD (3.19). All these comorbidities were robust in magnitude and statistically significant despite a relatively low number of subjects affected. The odds of receiving a diagnosis of Alcohol Dependence was 1.52 times higher in subjects who had a MDD diagnosis, than in those without this diagnosis, and the risk was 2.71 times higher in subjects with a lifetime diagnosis of Bipolar Disorder than in those who have not received said diagnosis.

C05. S05. Comorbidity between the psychiatric disorders and its association with the SERT polymorphism.

Table C5T05 summarizes the significant tetrachoric correlations between all the 16 mental disorders for the carriers of the (s) allele (N=348). Table C5T06 displays the significant tetrachoric correlations between all the 16 mental disorders for the non-carrier subsample (N=280). Anxiety disorders accounted for the majority of the significant correlations between disorders. Agoraphobia had significant correlations with Panic Disorder (0.4417), and with Social Phobia (0.4987) in the (s) carrier subsample (Table C5T05). Major Depressive Disorder was highly comorbid with Panic Disorder, as well as other anxiety disorders.

We examined the association between the (s) allele carrier status and the odds of being diagnosed a given comorbidity. When a subject has been diagnosed with two conditions (conditions A and B) in his/her lifetime, we describe this phenomenon as the presence of a comorbidity pair or dyad. In subjects that have been diagnosed with condition A, we calculated both in carriers of the (s) allele, and in non-carriers, the odds of being diagnosed with condition B. The ratios of these odds are displayed in Table C5T07. In several cases, the analysis could not be done due to insufficient subjects affected. The carrier status was associated with a significant increase in the odds for comorbidity in three dyads. For subjects diagnosed with Major Depressive Disorder, the carriers of the (s) allele, had a risk for being diagnosed with Social Phobia that was 5.13 times higher than the one of the non-carriers (OR: 5.13 (95%CI: 1.79; 14.74). For subjects diagnosed with Agoraphobia, the carriers of the (s) allele, had a risk for being diagnosed with Major Depressive Disorder that was 4.69 times higher than the one of the non-carriers (OR: 4.69 (95%CI: 1.11; 19.83). Finally, for subjects diagnosed with Social Phobia, the carriers of the (s) allele, had a risk for being diagnosed with Major Depressive Disorder that was 4.8 times higher than the one of the non-carriers (Odds Ratio = 4.80 (95%CI: 1.55; 14.84)

It is important to underline that the values of the odds ratios of a given comorbidity pair will be different according to the condition we consider first. As an example, a subject that was a

carrier with a diagnosis of Major Depressive Disorder had 5.13 times the risk of presenting with Social Phobia than the non-carrier subjects affected Major Depressive Disorder. However, if we consider the subjects who were carriers and have a diagnosis of Social Phobia, their risk of having Major Depressive Disorder was 4.8 times higher than the non-carriers (Tables C5T08-10)

C05. S06. Number of Multiple Diagnoses and Its Association with Gender and Age

We tallied the number of diagnoses received by individual participants during their lifetime. Table C5T11 displays the distribution of the number of lifetime prevalence diagnoses for the whole sample (N=847).

We examined the effect of gender, and age in the distribution of the number of lifetime diagnoses in the sample. Women had a higher burden of comorbidity than men (Table C5T12). Individuals over 44 years old had a higher burden of comorbidity as compared to younger participants (Table C5T13).

C05. S07. Association of SERT carrier status with Number of Diagnosis

Using Chi Square and Fisher's Exact Test, we examined the association of the SERT (s) allele carrier status with the prevalence of mental disorders. We examined the effect of the (S) allele carrier status in the overall number of lifetime diagnoses in the whole sample (C5T14). There were no significant differences in the distribution of the number of lifetime diagnoses between the (s) allele carrier and the non-carriers.

We subsequently grouped the subjects into dichotomous categories according to the number of lifetime diagnoses received in order to perform a logistic regression analysis that could allow us to adjust for possible confounding variables. In the first analysis, we divided the sample into a first group that included the subjects with one or more diagnoses, and a second group that included the subjects with no diagnoses (Table C5T15). For the second analysis, we divided the subjects into a first group that included the subjects who had received two or more diagnoses, and a second group that included the subjects who had received one or no diagnoses (Table C5T16). We performed logistic regression analysis, to determine the risk for the carrier subjects to belong to the category that presented with the higher number of diagnoses as compared to the risk for the non-carrier subjects. We adjusted the regression models for the effect of gender, age, marital status, and ethnicity. We were unable to find an association between the SERT (s) allele carrier status and the membership to the groups with a higher number of mental disorders (C5T15-16).

C05. S08. Summary and Conclusions

We explored the association of the SERT (s) allele carrier with prevalence and comorbidity of mental disorders using several analytical approaches.

We found a statistically significant association between the (S) allele carrier status and an increased risk of receiving a diagnosis of Panic Disorder in our study sample.

In addition, there was a strong association between the carrier status and the risk of being diagnosed with Bipolar Disorder, although the small number of affected individuals hindered the statistically significance of these findings

Anxiety disorders account for sizeable portion of the comorbidity burden in our sample followed by the comorbidity between mood disorders (MDD and Bipolar Disorder) and Alcohol Dependence.

We found a statistically significant association between the (s) allele carrier state and an increased risk for having a comorbidity between Major Depressive Disorder and Social Phobia, as well between Agoraphobia and Major Depressive Disorder.

We were unable to find any statistical association between the SERT (s) allele carrier status and the presence of an increased number of diagnoses, considered globally: namely, the carrier status appeared to have no association with the mental disorder morbidity burden.

CHAPTER 06 COMORBIDITY: MEASUREMENT CHALLENGES

C06.S01 Introduction

In this section we will evaluate the diagnostic and comorbidity patterns in our sample. Our analysis will be comprehensive and provide a quantitative measure of the degree of morbidity present in our study population. Our goal is not to attempt to find any latent factors that could explain the observed degree of symptom or diagnostic co-occurrence (C6R01), but to measure the diagnostic and comorbidity dynamics of our sample relying only on its observed or manifest variables. In order to transcend the mere description of the sample's characteristics, we will develop indicators to measure the overall burden of comorbidity of the individual psychiatric disorders and of the whole sample. These developed indicators, based on simple statistical principles, will also enable the comparison of the diagnostic and comorbidity patterns of the different disorders present within our sample. In addition, they could be used to compare diagnostic information between different samples. The overall aim of this investigation is to lay the groundwork for the measurement of the burden of comorbidity in different study samples that could be used in the future in larger observational studies and clinical trials.

C06.S02. The Effect of Comorbidity on Prevalence Estimates

Table C6T01A displays the unweighted lifetime prevalence estimates of the 16 selected mental disorders examined in our study sample. The column 01 displays the number of subjects in the sample diagnosed with each disorder, column 02 shows the unweighted lifetime prevalence estimates of each disorder as a percent (Number of Individuals Diagnosed with a Disorder/ Total Number of Subjects in the Sample x 100). Row 17, column 01 displays the Total Number of Diagnoses in the sample (N=868). This number is the result of the simple addition of

all the affected cases or diagnoses in our cohort. Row 17, column 02 displays the result of the quotient between the Total Number of Diagnoses in the sample, and the Total Number of Subjects in the sample (868 Diagnoses/ 847 Subjects= 1.0248). This translates into a total burden of mental illness in the study sample of 102.48 cases of mental disorders per 100 individuals in our population.

The Total Number of Diagnoses yields a tally (N=868) that is greater than the Total Number of Individuals in the sample (N=847). This rift between the number of diagnoses and the number of individuals becomes even more substantial when we consider that there is a large number of individuals in the sample who did not receive any diagnoses (N=355). If we exclude these 355 individuals from Total Number of Individuals in the Sample, we are left with a smaller group that we can categorize as the Total Number of Individuals Diagnosed (N= 492). These 492 are the number of individuals that are the source of the 868 diagnoses in the sample. This substantial difference between the number of individuals diagnosed and the number of diagnoses clearly indicates a high burden of comorbidity in our study sample. Thus, a more comprehensive examination of the extent of the burden of comorbidity becomes a crucial next step in order to better understand the distribution of the psychiatric morbidity in our study sample.

C06.S03. Methodological Issues

When an individual is diagnosed with a Condition A and a Condition B in his/her lifetime, we have identified a "comorbidity pair" or "comorbidity dyad". When we estimate the weight of the comorbidity phenomenon associated with the individual disorders, we need to count this comorbidity dyad once as a comorbidity of the Condition A, and a second time as a comorbidity of the Condition B. As we will describe throughout this chapter, this "double" count is crucial to

the understanding of the comorbidity phenomenon, as it enables us to evaluate the proper association between the individuals affected, the diagnoses, and the comorbidity burden.

As an example and to clarify the described concepts above, table C6T01B displays a hypothetical sample of 10 individuals. Individuals 01, 02 and 03 received no diagnoses. Individuals 04 and 05 have been only diagnosed with Condition A, individual 06 has been only diagnosed with Condition B. Individual 07 has been diagnosed with 2 conditions: Condition A, and B. Individual 08 has been diagnosed with 2 conditions: Condition A, and C. Individual 09 was diagnosed with 3 conditions: Conditions A, C, D. Lastly, Individual 10 has been diagnosed with 3 conditions: conditions B, C, and D. We can more thoroughly describe this hypothetical sample using some of the above described concepts as follows: total Number of Individuals in the sample (also known as Sample Size) =10. The total number of Individuals Diagnosed= 7. The Total Number of Diagnoses = 13. The Total Number of Comorbidities in the sample =16. Discriminating the comorbidity count by subjects: Individual 07 accounts for 2 comorbidities, Individual 08 accounts for 2 comorbidities, Individual 09 accounts for 6 comorbidities, lastly, Individual 10 accounts for 6 comorbidities. Discriminating the comorbidity count by diagnoses: Condition A accounts for 4 comorbidities, Condition B accounts for 3 comorbidities, Condition C accounts for 5 comorbidities, and finally, condition D accounts for 4 comorbidities. Figures 01A, 01B, and 01C display the counting of the comorbidity dyads by individual and by condition, according to the number of diagnoses present.

C06.S04. Three Complimentary Approaches for the Examination and Analysis of Comorbidity

In order to perform a comprehensive analysis of the comorbidity burden in our study sample, we will use three complementary approaches. In the first approach, we will examine the ratio between the number of comorbidities and the number of diagnoses in each individual

condition, as well as in the whole sample. In the second approach, we will examine the importance or impact of each comorbidity pair or dyad. This impact will be analyzed using three different vantage points or perspectives. In the first perspective, we will analyze the importance of each comorbidity dyad as measured by their overall sample prevalence. In the second vantage point, we will analyze the impact or weight of all comorbidity pairs to each of their integrating or member disorders. In the third vantage point of the second approach, we will obtain a measure of the strength of each comorbidity pair with respect to both of its integrating disorders. Lastly, in the third approach, we will examine the association between each individual disorder and the presence of individuals in the sample that received multiple diagnoses. For this last approach, we will stratify the individuals in the sample according to the number of diagnoses received (0, 1, 2 or more conditions) and we will then examine association of the prevalence of the individual conditions in each diagnostic stratum with the number of affected individuals in each diagnostic stratum.

C06.S05. Graphical Display of the Data: The Comorbidity Matrix Table

In order to have a thorough review of comorbidity between mental disorders in our sample, we displayed the sample's complete comorbidity and diagnostic information in Table C6T02A. We labeled this table as a Comorbidity Matrix. This table enabled us to calculate the number of comorbidities for each disorder and for the whole sample. We plotted in rows and columns 1 through 16 the individual mental disorders. The numbers that are displayed in each cell are the number of comorbidity pairs or dyads. These represent the number of subjects in the sample that were diagnosed in their lifetime with the two conditions that are listed in the heading of the row and the heading of the column that intersect in the selected cell. There are

30 comorbidity pairs representing 30 subjects in the sample that were diagnosed both with Alcohol Dependence and Social Phobia (row(r)01, column(c)08; as well as in r08, c01). There are 32 comorbidity pairs or dyads that represent 32 subjects diagnosed with Social Phobia and Major Depressive Disorder (r03, c08; as well as in r08, c03). The main diagonal represents the intersection of the identical disorders (e.g. Alcohol Dependence vs. Alcohol Dependence). These cells (r01, c01; r02, c02; … r16, c16) read all "N/A" for "Non- Applicable" as a condition cannot be comorbid with itself The cells of the row 17 from columns 01 through 16, as well as the cells of the column 17 from rows 01 through 16 display the total number of comorbidities for each individual disorder. Row 17 from c01 through c16 displays the total number of subjects diagnosed for each individual mental disorder (identical to the information displayed in row 01 of Table C6T01A). As an example, there were a total of 186 comorbidities tallied for those diagnosed with Major Depressive Disorder (r17, c03; and r03, c17). There were 152 subjects diagnosed with Major Depressive Disorder (r18, c03). Summarizing, we can posit that there were 152 individuals diagnosed with Major Depressive Disorder in the sample, and these 152 individuals were also diagnosed with an additional mental disorder on 186 occasions. The cell in row 17 and column 17 display the Total Number of Comorbidities in the sample (N=1146). The cell in the intersection of row 18 and column 17 displays the Total Number of Diagnoses in the sample (N=868).

Table C6T02A shows that most of the mental disorders have substantial comorbidity with each other. We can posit that comorbidity seems to be more the norm than the exception. Most of the individual disorders show a number of comorbidities that exceeds the number of subjects diagnosed with the primary condition. There are few empty cells. The only pattern we can see in the empty cells is the one that belongs to the identity diagonal (Disorder A vs Disorder A), and the cells that belong to the intersection of disorders that the Diagnostic and Statistical Manual of Mental Disorders (C6R02) instructs not to diagnose in the same subject

(e.g., Major Depressive Disorder or Dysthymic Disorder should not be diagnosed on a subject that has received a diagnosis of Bipolar Disorder).

C06.S06. First Approach: Examination of the Comorbidity to Diagnoses Ratio.

Our goal is to quantify the extent or burden of comorbidity for each individual disorder and for the whole sample in a manner that could be less influenced by the differences in prevalence of the individual disorders included in the analysis. For that purpose, we calculated a ratio between the number of comorbidities and the number of diagnoses for each condition, as well as for the total sample. We branded this ratio as the Comorbidity to Diagnosis Inflation Ratio (CDIR). We have chosen the term inflation, as it depicts the expansive effect that comorbidity can introduce in the diagnostic estimates. We borrowed this term from the field of economics as the causes and effects of comorbidity in psychopathology can be seen as analogous to the ones of inflation in the economy. Classical monetary theory (C6R03) posits that inflation can develop when the monetary authority of a country issues an excess of currency into its marketplace. This creates an excess of demand for the same number of goods that previously existed. Plainly described, there is more money available to buy the same number of goods. This excess of demand creates an increase in the price of goods. The practical effect is that the consumer will eventually need more currency bills or notes (plainly speaking more paper money) to buy the same number goods that a person was able to buy in the past for less. Analogous to this, the complexity of the field of psychopathology, and the shortcomings of our modern diagnostic classifications have conspired to create a condition that is similar to inflation. In order to increase coverage, our modern psychiatric classifications have issued an abundance of diagnostic labels to be used on a limited number of individuals. Each

newly created diagnostic label has an implicit value that can only become explicit when it is used to diagnose individuals. The excess in demand created by each new diagnosis lowers the value of the already established psychiatric disorders. The "old" or established diagnoses continue to be used concurrently with the new ones as they describe conditions that could be similar, but not identical, to the conditions covered by the new diagnoses. The end result of this diagnostic "excess" creates a new balance, in which there is a need to use a higher number of diagnoses than the one used in the past to complete the "purchase" of an individual psychopathology (or of the community psychiatric burden if considered at a macro level).

C06.S07. The Comorbidity to Diagnoses Inflation Ratio (CDIR)

The Comorbidity to Diagnoses Inflation Ratio (CDIR) of the whole sample is the quotient between the Total Number of Comorbidities (N=1146) and the Total Number of Diagnoses (or Subjects Diagnosed) (N=868). The CDIR for the whole sample yielded a value of 1.32. This value indicates that there is a ratio of 132 comorbidities per 100 diagnoses in our sample. We later standardized the CDIR of each disorder using the CDIR of the whole sample as denominator. With the standardized CDIR (SCDIR) we were able to clearly identify those conditions that exceeded the value of the total sample in their comorbidity burden. By standardizing the information, we were more confident in obtaining an instrument that could yield results that could be used to compare between conditions. By examining the table C6T02A, we can clearly see that the Anxiety Disorders had the highest burden of comorbidity in the sample. Obsessive Compulsive Disorder, with a CDIR of 2.5, was the psychiatric condition with the highest value. This means that for every 10 diagnoses of Obsessive Compulsive Disorder (OCD), there were 25 comorbidities of OCD with other psychiatric disorders. The SCDIR for OCD yielded a value of 1.89. This value indicates that OCD had a comorbidity burden that was 89% higher than the one of the overall sample. Following OCD, in order of

decreasing burden, there were three anxiety disorders, Agoraphobia: CDIR = 2.12 and SCDIR= 1.61; Social Phobia: CDIR=1.65 and SCDIR=1.25; and, Panic Disorder: CDIR= 1.61 and SCDIR= 1.22.

C06.S08. Second Approach: Examination of the Impact of Each Comorbidity Dyad

As mentioned before, in this second approach we will analyze the importance of each comorbidity pair or dyad. The impact of a comorbidity dyad can be analyzed from the three different vantage points already described.

C06.S09.Second Approach, First Vantage Point: Examination of the Impact of Each Comorbidity Dyad for the Whole Sample

The goal of the first vantage point is to determine the weight of each comorbidity pair for the sample as a whole. If we define a comorbidity dyad as integrated by Condition A and Condition B, in this approach we examined the probability or prevalence of the joint probability of Condition A and Condition B (PA∩B) in the whole sample. The analysis from this vantage point provides us information about the comorbidity dyads that are more frequent in the sample. In a prevalence study with careful sampling methodology, this approach might provide information about the impact of a particular comorbidity for the population as a whole. Table C6T02B displays the prevalence of the comorbidity pairs as a percentage to the total number of individuals in the sample (N=847). The comorbidity pair with the highest prevalence (0.0484 or 4.84%) was composed by the individuals diagnosed with both Major Depressive Disorder and Alcohol Dependence (r01, c03 and r03 c01). The second highest pair was the one comprised by the individuals diagnosed with both Major Depressive Disorder and Social Phobia (r03, c08 and r08, c03) presenting with a prevalence in the sample of 0.0378 or 3.78%. All these comorbidity

dyads included the mental disorders with the highest prevalence in the sample. We were able to detect a pattern in which the absolute prevalence of each comorbidity pair was largely explained by the prevalence of the disorders that composed it. This approach might prove useful to detect which comorbidity is important from a population perspective.

C06.S10.Second Approach: Second Vantage Point. Examination of the Impact of the Comorbidity Dyads on Each of Its Integrating Disorders

The second vantage point examined the impact of the comorbidity pairs on each of their member disorders. If we define a comorbidity dyad as composed by Condition A and Condition B, our analysis in this approach yielded two different values. The first value can be defined as the probability of Condition B, given condition A. It can be estimated by dividing the joint probability of Condition A and Condition B (prevalence of the comorbidity) by the probability of Condition A (or prevalence of Condition A) (PA∩B / PA). The second value can be defined as the probability of Condition B given Condition A. It can be estimated by dividing the joint probability of Condition A and Condition B divided by the probability of Condition B (PA∩B / PB). In layman terms, this approach will inform how common it is to suffer from Condition B for a patient that is already affected by Condition A (and vice-versa). The two values provided will be less influenced by the overall prevalence of the Conditions A and B. In addition, the two values can differ greatly. As an example, there are 32 subjects in the sample that presented with Major Depressive Disorder and Social Phobia (r03, c08; and r08, c03). This comorbidity dyad was one of the most prevalent in the sample (32/ 847= 0.0378), though it only represents 21.05% of the total diagnoses for the subjects with Major Depressive Disorder, and the 32.00% of the total of diagnosed with Social Phobia. In contrast, there are 9 subjects diagnosed with the comorbidity

between Alcohol Dependence and Bipolar Disorder in the sample (r01, c04; and r04, c01). Although this comorbid dyad had a relatively low overall prevalence in relation to the total sample (9/847= 0.0106), it represents 40.91% of the diagnoses for Bipolar Disorder. Due to the difference in prevalence between the 2 disorders, it only represents 5.08% of the total diagnoses of Alcohol Dependence. The high burden that this comorbidity dyad had on Bipolar Disorder provided evidence that should be addressed at a research and at a clinical level. The information this approach provided is germane to the field of psychopathology. A comorbidity that has such a high impact in the prevalence of any given disorder may indicate a common etiological mechanism, or a measurement problem (in this example it can bring into consideration whether alcohol abuse should be considered a symptom criteria for Bipolar Disorder). If this high degree of comorbidity is consistent with other studies, any clinical institution dealing with patients affected with Bipolar Disorder should be aware of the increased risk of their patients to suffer from Alcohol Dependence as well. In contrast, due to the differences in prevalence rates between the two conditions, this comorbidity dyad was not highly important for those affected with Alcohol Dependence. Thus, when dealing with a population of primary Alcohol Dependence patients, Bipolar Disorder might not be in the main focus when considering research and clinical interventions. The unequal impact that a given comorbidity pair can have on its integrating disorders should be considered when selecting the source of the population in the sampling process. Any sample that derives from a clinical source should be controlled for the unequal odds of a second disease that some individuals bring in to the sample.

In order to capture the impact of the comorbidity dyads for each of their integrating disorders, we designed Table C6T02C Comorbidity and Diagnosis Composition as Row Percentage. Rows 01 through 16 display the comorbidity composition (as percentages) of the mental disorders that appear in the heading of each row. For example, row 03 clearly displays

how the rest of the mental disorders impact on the comorbidity make-up of Major Depressive Disorder. In probability terms, the value in each cell represents the conditional probability of the condition that appears in the heading of the column given the condition that appears in the heading of the row. As an example, the conditional probability of Social Phobia, given the subject has Major Depressive Disorder is 32/152= 0.2105 or 21.05% (r03, c08). On the other hand, the conditional probability that a subject has Major Depressive Disorder given he/she has Social Phobia is 32/100= 0.32 or 32% (r08, c03). The table is useful as it can quickly display the impact of all comorbidity pairs on each of its member disorders.

C06.S11. Second Approach: Third Vantage Point. Examination of the Strength of Each Comorbidity Dyad with respect to both of Its Member Disorders

In this third vantage point, our goal was to obtain a single measure of the strength of the association between each comorbidity dyad and its two integrating conditions. In order to obtain a quick summary measure, we created a ratio of probabilities. We labeled this indicator as a Ratio of Conditional to Marginal Probabilities (RCMP). This ratio holds several statistical characteristics and it is relatively easy to compute for all conditions using the Comorbidity Matrix Table as a source.

The results of the RCMP for all comorbidity dyads are displayed in table C6T02D. The values in the cells can be described in several ways. As an example, we can state that comorbidity dyad is integrated by Condition A and Condition B. The values can be seen as the joint probability of Condition A and Condition B divided by the product of Condition A and Condition B (P A∩B / PA×PB). This ratio can also be expressed as PA/B / PA the conditional probability of the Condition A given the Condition B divided by the probability of the Condition A.

In probability terms, the ratio of PA/B /PA is identical to PB/A / PB, the conditional probability of Condition B given A divided by the Probability of Condition B, this feature makes the value of the indicator the same whether we are considering the impact of the comorbidity pair on Condition A or Condition B. In addition, this indicator can also be expressed as the observed prevalence of the comorbidity pair divided by its expected prevalence. The observed prevalence of the comorbidity dyads is identical to the Joint Probability Prevalence, expressed in Table C6T02B as a prevalence proportion. The expected prevalence calculated as computed as (Prevalence of Condition A) x (Prevalence of Condition B) / Sample Size).

The range of values for the RCMP span from 0 to the inverse of the prevalence proportion of condition member of the dyad with the highest prevalence. A value of 0 indicates that the dyad's member disorders share no common cases. From 0 through 1 the value indicates that the 2 conditions members of the comorbidity dyad have a negative tendency to co-occur. A value of 1 indicates that the two conditions have a neutral tendency towards comorbidity. In probability terms a value of 1 indicates that the ratio of the conditional probability of Condition A given B divided by the marginal probability of the Condition A is identical (PA/B / PA =1). In probability terms, this indicates that Condition A and Condition B are independent, and all co-occurrence between them is due to chance alone. A value of the RCMP higher than 1 indicates that the conditional probability of Condition A given B is higher than the marginal probability of Condition B. In observed vs expected language, a value over 1 indicates that the prevalence of the observed comorbidity of Condition A and Condition B (PA∩B) is higher than the prevalence that should be expected if Conditions A and B are fully independent (PA×PB / Sample Size). Thus, a value higher than one suggests that there is an association of the two conditions that is higher than the one expected by chance alone.

In table C6T02D, r01, c03 and r03, c01, we can read the value of 1.29. This can be described as the probability of a diagnoses of Major Depressive Disorder in subjects diagnosed

with Alcohol Dependence divided by the probability of a diagnoses of Major Depressive Disorder in the whole sample. It can also be described as the probability of a diagnoses of Alcohol Dependence in individuals already diagnosed with Major Depressive Disorder divided by the probability of Alcohol Dependence in the whole sample.

Table C6T02E, reports the Odds Ratio (OR) values of all comorbidity pairs (those that had common cases). If we compare the OR estimates to the Ratio of Conditional vs Marginal Probabilities, we can see that the RCMP values have the same direction that the ORs, being somewhat more conservative. The ORs have the added advantage of a significance testing, although they are far more time demanding in their execution than the RCMP. The RCMPs are easily calculated by row and column operations and can be used in a descriptive initial approach to examine the diagnostic patterns of a given sample

If we examine tables C6T02D and C6T02E we can see that several anxiety disorders, including Panic Disorder, Agoraphobia, Social Phobia, Obsessive Compulsive Disorder, and Generalized Anxiety Disorder had both the highest number of comorbidities and the highest value for both the RCMPs and the ORs. These conditions are comorbid with the disorders s with highest prevalence (Major Depressive Disorder, Social Phobia, Alcohol Dependence), in addition, these conditions are highly comorbid with each other. The RCMP values for the dyads of these conditions are the highest as their upper value of their range is determined by the inverse of their prevalence proportion. As the prevalence proportions of these conditions are low, their inverse is high when compared to the ones of more prevalent conditions.

C06.S12.Third Approach: Analysis of the Association between the Prevalence of Each Individual Disorder and the Presence of Multiple Diagnoses

In the previous approaches, we have centered our analyses in the prevalence of diagnoses and comorbidities without consideration to the affected individuals. As these affected individuals are the source of all clinical information, the analysis of the association between affected individuals and diagnoses is a crucial step towards a better understanding of comorbidity phenomenon. In this third approach, we will analyze the patterns of multiple diagnoses in the sample, and attempt to determine the relationship between individuals diagnosed, diagnoses, and comorbidities for all the individual disorders as well as for the whole sample.

We stratified the individuals of the whole sample according to the number of mental disorders that they have been diagnosed. We divided the subjects into 7 diagnostic groups, as the highest number of mental disorders diagnosed in a single individual was 6. The first Diagnostic Group (DG0) included 355 individuals that had received no psychiatric diagnosis in their lifetime. The second Diagnostic Group (DG1) comprised 255 individuals who had received only one mental disorder diagnosis (any of the 16 mental disorders), the third Diagnostic Group (DG2) included 143 subjects who had received any 2 mental disorder diagnoses in their lifetime, the fourth Diagnostic Group (DG3) comprised 61 subjects who had been diagnosed with 3 mental disorders, the fifth Diagnostic Group (DG4) included 22 subjects who had each received 4 mental disorder diagnoses in their lifetime, the Diagnostic Group (DG5) or stratum comprised 10 subjects who had each received 5 diagnoses, and the final and seventh Diagnostic Group (DG6) included only one member, who was diagnosed with 6 disorders.

Table C6T03A details this grouping or stratification of the 847 individuals in the sample. Column 01 displays the individuals that did not receive any psychiatric diagnosis. Columns 02 through 07, rows 01 through 16 display the number of subjects diagnosed in each diagnostic group, the cells of column 08 display the total diagnoses for the individual mental disorders. Row 17 contains the number of diagnoses accrued by each diagnostic group (DG0=0,

DG1=255, DG2=286, DG3=183, DG4=88, DG5=50, and DG6=6) and by the total sample (N=868). Row 18 displays the number of individuals that received a diagnosis in each group (DG0=0, DG1=255, DG2=143, DG3=61, DG4=22, DG5=10, and DG6=1) as well as in the total sample (N=492). Row 19 displays the number of individuals in each group (as discussed above) and in the total sample (N=847). The information in these rows helps in a more comprehensive understanding of the dynamics or patterns behind individuals and diagnoses in the sample.

In order to further understand the dynamics of comorbidity, we presented the diagnostic counts on table C6T03A as row percentages in table C6T03B. Considering the cells of rows 17 through 19, columns 01 through 07, we see that comorbidity entails a pattern of under-representation of a majority of the individuals of the sample. This under-representation is due to the focus placed on the number of diagnoses or clinical data, ignoring the number of individuals that these clinical data represent. As an example, DG1 contains 51.83% (r19, c02), of the total individuals of the sample that have received a psychiatric diagnosis. Paradoxically, this group only represents 29.38% (r17, c02) of the total diagnoses present in the sample. If we combine the values of DG0 and DG1, the comparisons become even more striking. By adding the values of the cells for row 19 and columns 01 and 02 (41.91 + 30.11 = 72.02%). We can state that 72.02% of all individuals in the sample have received either one or no diagnoses. This sizable part of the sample is providing only 29.38% of all the number of diagnoses in the sample. We can state that the sample is ruled by a 70/30 ratio. There is a 70% of the sample that provides 30% of clinical information, and vice-versa. The importance of the G0 is crucial in this ratio. The 29.38% (r17, c02) also represents the percentage of all diagnoses originated from individuals who do not have any additional mental disorders. These should be considered the "pure cases" free of any comorbidity. We can affirm now that these "pure cases" represent only a minority, or less than a third of all diagnosed conditions in the sample.

If we consider the values for DG1 for the psychiatric conditions individually, we can appreciate that Alcohol Dependence (38.985), Alcohol Abuse (50%), Major Depressive Disorder (32.89%), Bipolar Disorder (36.36%), Dysthymic Disorder (33.33%) Depressive Disorder NOS (38.89%), have row percentages that largely exceed the value of the whole DG1 (29.38%). We can posit that the individual disorders that appear in DG1 at a rate higher than the average have a low propensity to be comorbid. On the opposite end, we can state that the disorders that appear at a higher rate than the average in DG3 through DG7 have a tendency towards comorbidity. From columns 04 through 07 in table C6T03B we see that that Agoraphobia, Social Phobia, Obsessive Compulsive Disorder, and, Generalized Anxiety Disorder are over-represented in the groups with high number of diagnoses. We can postulate that these mental disorders are those with the highest comorbidity propensity in the sample (that is consistent with the CDIR results). Thus, we need a proper tool to measure this over-representation in order to accurately measure the comorbidity burden in each individual condition included in the sample.

C06.S13.Proposed Method: Adjustment of the Diagnostic Information and Ratio Method

Our findings suggest that the burden of comorbidity could be defined as a state of over-representation of the clinical information from subjects with a high number of diagnoses. We propose a two-step method that could measure this over-representation. In the first step, we would adjust the clinical information to the individual level, creating a scenario that could act as a counterfactual state of this over-representation. In its second step, the method will measure the difference between the original diagnostic information with the one obtained by this adjustment method. The adjustment consisted in granting to every individual in the sample only one diagnostic allowance. This allowance or quota would have the same weight for every individual in the sample, whether they were found to have one mental disorder, or many. If an individual had two diagnoses, the adjustment would reduce the value of each diagnosis to one

half. The second step would perform a ratio of the original diagnostic information to the one that resulted from this adjustment. The working premise was that a condition with a high burden of comorbidity would have a higher number of subjects affected in the diagnostic groups that allocated individuals with multiple diagnoses. This would translate into a more profound effect of the adjustment. Thus, the value of the original over adjusted ratio would be the highest on the conditions that had the highest degree of comorbidity.

Using Major Depressive Disorder as an example, there are 152 subjects that had a lifetime prevalence diagnoses for Major Depressive Disorder. This value is the result of the addition of 50 diagnoses from individuals in DG1, 48 diagnoses from individuals in DG2, 33 diagnoses from individuals in DG3, 13 diagnoses from individuals in DG4, 7 diagnoses from individuals in DG5, and 1 diagnosis from individuals in DG6. As the individuals in DG2 have each provided 2 diagnoses to the analysis, the adjustment method calls for dividing their information by 2, reducing the value of each diagnosis originated in the DG2 to ½. This reduction will be done in a progressive fashion until we reach the DG with the highest diagnoses per individual. In our sample, every diagnosis of the DG6 subjects will be weighted down to down to 1/6. The result of this method would adjust the lifetime prevalence count for Major Depressive Disorder to 89.82. By calculating the ratio of the cumulative adjusted diagnoses to the cumulative or total unadjusted diagnoses of MDD, we can state that the adjustment in Major Depressive Disorder deflated 59% of all diagnostic information (89.82 / 152=0.59). The value of the ratio of unadjusted diagnostic information over adjusted diagnostic information was 1.69.

Table C6T03C displays the results of this deflationary adjustment method. Column 01 displays the unadjusted number of diagnoses. Column 02 displays the same values after the adjustment method. Column 03 displays the proportion of the unadjusted estimate that remained after the adjustment, for each disorder, and for the whole sample. Column 04 displays

the ratio of unadjusted vs adjusted diagnoses. Column 05 presents the previous ratio, adjusted by ratio the total sample.

C06.S14. The Diagnostic Inflation Ratio (DIR)

As we can see in table C6T03C, the adjustment had the goal to shrink the Total Number of Diagnoses (N=868) (r17, c01), to be identical to the Total Number of Individuals Diagnosed (N=492) (r17, c02). The "deflated" diagnostic information proportion left after the adjustment for the total sample was 0.57 (r17, c03) (this is analogous to positing that the adjustment or deflation for the diagnostic information of the whole sample was 43.32%). The ratio between unadjusted and adjusted for the whole sample, that we will call for consistency purposes, the Diagnostic Inflation Ratio (DIR) was 1.76. This value can also be obtained by dividing the Total Number of Diagnoses (N=868) by the Total Number of Individuals Diagnosed (N=492). In essence, we can state that this value represents the ratio between the Diagnoses and the Individuals Diagnosed. In probabilistic terms the DIR is the average or expected number of diagnoses that we would find in an individual that has been diagnosed with a mental disorder in his/her lifetime, selected at random from the sample. The value of 1.76 for the DIR of the whole sample means that we can expect that any individual from the sample selected at random from DG1 through DG6 would have an expected number of 1.76 diagnoses. This ratio can provide a quantitative indicator of the comorbidity burden of the sample that could be compared with values obtained from other samples, as well as between disorders within the sample. It can be also used to compare the effect of including or excluding any individual or group of mental disorders from sample. . The DIR of OCD equals to 2.82. This estimate indicates that if any

individual in the sample diagnosed with OCD is selected at random (from DG1 through DG6), this individual will be affected, in average, by 2.82 conditions.

In order to compare the DIR between disorders, we standardized the DIR of each disorder, using the DIR of the whole sample as norm (same method we used for the CDIR). The standardized ratios in column 05 indicate that the anxiety disorders (Panic Disorders DIR= 2.07, SDIR= 1.18, Agoraphobia DIR=2.45, SDIR=1.39, Social Phobia DIR=2.11, SDIR=1.19, Obsessive Compulsive Disorder DIR=2.82, SDIR=1.6, and, Generalized Anxiety Disorder DIR=1.99, SDIR=1.13 were the conditions that suffered the most extreme adjustments, indicating that these are the mental disorders that have the highest propensity towards comorbidity. These results are consistent to the results obtained by the Comorbidity to Diagnosis Inflation Ratio.

C06.S15. A Proposed Measure of Comorbidity: The Comorbidity Inflation Ratio (CIR)

We wanted to measure the relationship between the adjusted number of diagnoses (that was deflated to be identical to the number of individuals diagnosed in the sample) and the number of comorbidities. For that purpose we calculated a ratio between the number of comorbidities for each disorder and the adjusted number of diagnoses, and the ratio between the Total Number of Comorbidities and the Total Number of Individuals Diagnosed for the whole sample. For consistency purposes, we called this measure the Comorbidity Inflation Ratio (CIR). This crude measure is intended to quantify the average or expected number of comorbidities per individual diagnosed. In our sample the CIR was 2.33 (r17, c07). This value indicates that any individual selected at random from the sample (from DG1 through DG6) will have an expected value of 2.33 comorbidities based on the selected mental disorders. This value will be

different if we make it contingent to a particular condition. As an example, any individual with diagnoses of OCD picked up at random will have an expected number of comorbidities of 7.05.

We later normalized the CIR of the individual disorders with the CIR of the total sample. This enabled us to compare the individual disorders. The results of the Comorbidity Inflation Ratio (CIR) and its standardized version (C6T03C column 08) are consistent with the findings for the Diagnostic Inflation Ratio. The anxiety disorders are the conditions that have the highest values of CIR and SCIR. Specifically, Panic Disorder (CIR: 3.36, SCIR: 1.43), Agoraphobia (CIR: 5.20, SCIR: 2.30), Social Phobia (CIR: 3.47, SCIR: 1.49), Obsessive Compulsive Disorder (CIR: 7.05, SCIR: 3.02) and Generalized Anxiety Disorder (CIR: 3.50, SCIR: 1.50) are the individual conditions whose comorbidity burden largely outweigh both the rest of the disorders and the average burden for the whole sample.

The cells in column 09 display the unadjusted lifetime prevalence estimates for each disorder (rows 02 through 17) (identical to the ones of Table C6T01A), and the overall burden for whole sample (c06, r18). The cells in column 10 display the corresponding estimates after the proposed adjustment. These adjusted lifetime prevalence estimates could serve as a good reference of a counterfactual state in which comorbidity would be restricted in the classification.

C06.S16. Significance Test for Individual Disorders

In the previous section, we proposed the Diagnostic Inflation Ratio (DIR), and specifically its standardized version (SDIR), as a measure of the comorbidity burden of each individual mental disorder in the sample. We believe that these instruments could be useful in describing the comorbidity, although they lack a measure of statistical significance.

In order to establish this statistical significance, we performed a chi square and exact test on the distribution of each individual disorder. Table C6T03D displays the diagnostic

distribution of the individuals diagnosed with Alcohol Dependence across the diagnostic strata. We performed Chi Square and Fisher Exact Tests for each disorder, analyzing the diagnostic counts of each disorder in the DG1 through DG6 against the rest (obtained by subtracting the diagnostic counts of the disorder under examination from the Number of Total Diagnoses in each DG). The results are very consistent with the results of the Diagnostic Inflation Ratio. Disorders that are under 0.80 or over 1.10 of the standardized DIR have significant results in the Fisher's Exact Test. In Table C6T03E we see that Alcohol Dependence, Agoraphobia, Social Phobia, Obsessive Compulsive Disorder, and Generalized Anxiety Disorder have all significant results in both the Chi Square and the Fisher's Exact Tests. These results indicate that the diagnostic distribution across the diagnostic groups or strata of these disorders differs significantly from the distribution of diagnoses of the sample. In the case of Alcohol Dependence (SDIR: 0.89), the results indicate that the individuals diagnosed with this condition tend to have less comorbidities (this be less frequent in DG3-DG6). In the case of the other disorders, the results indicate that these conditions tend to have relatively more individuals diagnosed in the DG3-DG6 than the sample as a whole.

C06.S17.The Dynamics between Diagnoses and Comorbidities in a Sample

Table C6T04 displays the information on diagnosis and comorbidity by diagnostic groups or strata. This table is essentially identically to the Table C6T03A with the addition of the information on comorbidities in the strata and in the whole sample to the right of the diagnostic information. This table enables visualization of the relationship between individuals, diagnoses, and comorbidities for the whole sample as well as for the each individual mental disorder.

The cells of row 20 display the number of individuals in each diagnostic group. The cells of row 19 display the number of individuals diagnosed in each diagnostic group. We see that the relationship between the two is simple. The difference between them is that the former counts the individuals that have received no diagnosis (DG0). These individuals could have an importance for the overall prevalence estimates but have no bearing in this analysis, as they do not contribute any diagnostic information. Thus, we should consider the Total Number of Individuals Diagnosed (N=492) as the primary or fundamental total count. The cells of row 17 from columns 01 through 14 display the number of diagnoses for each diagnostic group. In r17, c15 we see the Total Number Diagnoses (sometimes called subjects affected, or subjects diagnosed) (N= 868). Row 18 from columns 01 through 15, displays the number comorbidities for each diagnostic group. In r18, c16 we can see displayed the Total number of Comorbidities (N= 1146). Thus, while rows 17 and 18 enables us to see the progressive accumulation of diagnoses and comorbidities in the sample, row 19 displays the number of individuals in each strata that is the source of this clinical information. FigureC6F02 shows the distribution of the number of diagnoses, the number of comorbidities, and, the number of Individuals in the sample, stratified by Diagnostic Group or Strata.

C06.S18. Dynamics of the Relationship between Total Number of Individuals Diagnosed, Total Number of Diagnoses and Total Number of Comorbidities. Random and Fixed Elements

The relationship between the Total Number of Individuals Diagnosed with the Total Number of Diagnoses and the Total Number of Comorbidities can be understood as three different but related random probability distributions. These distributions share random elements

that pertain to each sample analyzed, and fixed probabilistic elements that are particular to each distribution, and are universal to all samples.

The random elements include: 1) the number of diagnostic groups or strata that in probability terms translates as the number of possible outcomes in a random distribution; and, 2) the number of individuals in each diagnostic strata that in probability terms translates into the probability of each outcome (as proportionate to the total number). As we have already mentioned, these elements are dependent on the particular sample that we are analyzing and are shared by the three distributions.

The fixed elements correspond to values attached to each outcome. These values are specific to each distribution and are permanent, regardless of the samples under study. While the number of outcomes is contingent on the sample under examination, the values attached to each of these outcomes for these 3 distributions are a function that can be predicted.

In the distribution of the Total Number of Individuals Diagnosed, the value attached would be one for all possible outcomes (as only one diagnosis is allowed for each Diagnostic Group). In the distribution concerning the Total Number of Diagnoses, the value of each possible outcome is identical to the Modal Diagnoses of the Diagnostic Group or Strata (DG1= 1, DG2= 2, DG3= 3). Finally, in the distribution of the Total Number of Comorbidities, the value of each possible outcome equals to (Modal Diagnosis x Modal Diagnosis Diagnosis-1).

In our sample, the distribution of individuals diagnosed has 6 possible outcomes (DG1-DG6). From Total of Individuals Diagnosed (n=492), the probability of picking an individual that has exactly 3 lifetime prevalence diagnoses is 0.12 (61/ 492=0.124). The probability of selecting an individual that has exactly 4 diagnoses is 0.04 (22 /492 = 0.045). All these are random elements, contingent on the sample. The number of outcomes and probability for each outcome would be different in other samples. In contrast, the value attached to each outcome is a fixed

element. An individual chosen at random with 3 diagnoses would account for 6 comorbidities. This would be true for any sample. Figure C6F03 displays the relationship between the number of diagnoses and the number of comorbidities by Diagnostic Group or Stata. For a comprehensive explanation of the mathematical basis of the relationship between diagnoses and comorbidities in a sample, see Appendix 01.

C06.S19.Summary and Conclusions

In this section we evaluated the diagnostic and comorbidity patterns of our study cohort. Our overall aim was to measure the comorbidity burden of the individual disorders and of the whole sample. In order to achieve this goal, we developed indicators based on simple probability principles that could enable a quantitative comparison of the diagnostic and comorbidity patterns that the different disorders present within our sample.

The mean or expected value of diagnoses in our study sample (DIR) was 1.76, the mean or expected value for the number of comorbidities for a subject picked up at random was 2.33 (CIR). Our findings suggest that anxiety disorders are the psychiatric conditions with the highest degree of comorbidity burden in our study sample.

The indicators presented could have several uses and be useful in different scenarios. Table C6T05 lists the proposed measures, with a brief description. These measures can be used in the comparison of different samples, or, of subgroups in the same sample, as we have done in comparing the carriers of the (s) allele with the non-carriers in our study sample (Appendix 02).

The clinical implications, as well as clinical uses, will be discussed in more detail in the conclusion chapter.

CHAPTER 07. PART 1.

ANALYSIS OF TIME-TO-DIAGNOSIS. ASSOCIATION WITH THE SEROTONIN TRANSPORTER GENE POLYMORPHISM

C07.P01.S01. Aims

In this section, we will examine the difference in the reported time that the affected subjects required to achieve full criteria for selected diagnoses. In particular, we will investigate whether the carriers of the Serotonin Transporter Gene (SERT) short (s) allele had any significant differences in the time (age) to meet criteria for the selected mental disorders as compared to the subjects who were not carriers for this genetic polymorphism in our study sample.

In order to achieve this goal, we will use several statistical techniques to examine the "time to event" variable. In our previous analyses, we examined whether the participants were affected by the individual mental disorders using a lifetime prevalence approach. One important limitation of this approach, is that it ignores the difference in ages of the participants. Every affected subject is equally counted in the numerator, and all subjects are equally included the denominator. Thus, the lifetime prevalence estimates disregard the differences in age of the participants, disregarding the variations of the time at risk for each individual, to develop the disorders under study. By using statistical techniques that focus on the time to event, in this case time to diagnosis, we aim at correcting the limitation of the previous analyses.

C07.P01.S02. Analytical Approach

We used the Kaplan-Meier (Product Limit) Approach. Subjects started to accrue exposure time at the moment of their birth. The follow-up time ended at the time the client had the "event" or "failure" of interest: namely, the reported age when they met criteria for the selected disorder. Subjects who never met criteria for the selected disorder at the moment of the study were censored at the age of the interview. We used this technique for each selected disorder in which we had information of the age of onset in the sample. By calculating the quotient between the number of events and the total person-years accrued by the subjects, we were able to obtain an Incidence Rate for each condition.

We later calculated the events and exposure time both for the carriers of the SERT (S) allele and for the non-carrier subjects, and obtained a separate Incidence Rate for both groups in each condition. We calculated ratio a between the Incidence Rates of carriers and non-carries for each condition with the goal to determine whether there was an association of the carrier state with the development of the examined mental disorder.

We later calculated Log-Rank tests for each condition to estimate whether the survival curves (in our case the time to diagnosis) were different between groups: namely, whether the carriers had a different time trajectory in attaining each diagnoses under examination

Finally, we performed a Cox Proportional Hazards Regression Analysis for each condition. This approach enabled us to examine the association the SERT (s) allele carrier to the survival time (in our case, time to attain diagnosis). The Cox Proportional Hazard Regression model also allowed us to adjust the hazard estimates by potential confounding variables: namely, gender, ethnicity, and marital status. Thus, using this technique we were able to obtain a Hazard Ratio between the carrier and non-carrier participants for each condition examined, both unadjusted and adjusted for the aforementioned variables. Lastly, we examined whether our analysis for each condition met the proportional-hazards assumption required in the Cox Regression Model.

C07.P01.S03. Findings Time to Diagnosis

Table C7T01 summarizes the estimates the total number of failures (Lifetime Prevalence Diagnoses), Total Person-Years, and corresponding Incidence Rate per 1000 person-years for each included mental disorder for the whole sample (N=847), the SERT (S) Allele Carrier Subjects (LS+ SS) (N=336), and lastly for the SERT (s) Allele Non-Carrier Subjects (LL) (N=226).

Table C7T02 summarizes the estimates of several analyses done comparing the SERT (s) allele carrier with the non-carrier subgroups (Incidence Rates Ratios, Long Rank Tests, as well as the unadjusted and adjusted Cox Proportional Hazards Regression Analysis results)

The SERT (s) allele carrier status was associated with a 2.7 times higher risk for receiving a diagnosis of Panic Disorder (Incidence Rate Ratio: 2.70 (95% CI: 1.13-7.42). For Panic Disorder subjects, this difference between carriers and non-carriers was also observed in the Log-Rank Test, and in the unadjusted Hazard Ratio. The Hazard Ratio, adjusted for gender, ethnicity, and marital status, was of borderline significance (Adjusted Hazard Ratio: 2.35 (95% CI: 1.00-2.51) (Table C7T02).

In addition, the SERT (s) allele carrier status was associated with a significant 87% decrease in risk for receiving a diagnosis of Obsessive-Compulsive Disorder (Incidence Rate Ratio: 0.13 (95%CI: 0.00-0.99). For Obsessive-Compulsive Disorder, this difference between carriers and non-carriers was also significant using the Log-Rank Test, and both the unadjusted Hazard Ratio, as well as for the Hazard Ratio adjusted for gender, ethnicity, and marital status (Adjusted Hazard Ratio: 0.11 (95% CI: 0.01-0.95) (Table C7T02).

C07.P01.S04. Conclusions on Time to Diagnosis

We explored the association of the SERT (s) allele carrier with the time to achieve full criteria for the selected diagnoses in our study participants using different survival analysis approaches.

We found a statistically significant increased risk for Panic Disorder in the carrier group as compared to the non-carrier. In addition, we found a statistically significant "protective" effect of the carrier status in the diagnosis of Obsessive Compulsive Disorder.

CHAPTER 07. PART 02.

USE OF PSYCHOTROPIC AGENTS. ASSOCIATION WITH THE SEROTONIN TRANSPORTER GENE POLYMORPHISM

C07.P02.S01. Aims

In this section, we will explore the use of medications in our study sample and its association with the SERT (s) gene polymorphism.

At the time of the interview, the subjects were queried about their current use of several psychotropic agents. These included antidepressants, anti-anxiety agents, hypnotic agents, antipsychotic agents, and anti-manic agents.

C07.P02.S02. Analytical Approach

Using Pearson's Chi-Square and Fisher Exact Tests, we explored the association of the carrier state for the Serotonin Transporter Gene (SERT) short (s) allele with the use of these medications.

Due to the limited sample size, we created cumulative categories to improve the power of the analyses. We combined anti-anxiety and antidepressant agents into one category. Finally, we combined all psychotropic agents that were included in the interview into one category to explore if there was any association between the use of any psychotropic agent with the SERT (s) gene polymorphism.

C07.P02.S03. Use of Psychotropic Agents in the Sample

Table C7T03 summarizes the findings of our analyses. Antidepressant agents were the most widely prescribed for our subjects (8.85 per 100 subjects), followed by anti-anxiety agents (4.25 per 100 subjects). The overall use of psychotropic agents in the sample (including all types of psychotropic agents) was equal to 10.51 per 100 subjects.

C07.P02.S04. Association of Psychotropic Use with SERT (s) Polymorphism

The ratio of medication use in the SERT (s) allele carriers versus non-carriers was not significant for any of the psychotropic agents included in the study. When examining the overall psychotropic use, the SERT carrier status was not associated with an increase use of these medications, as compared to non-carriers.

C07.P02.S05. Summary: Use of Medications

We explored the association of the SERT (s) allele carrier with the use of psychotic agents in our study participants using univariate statistical approaches.

We were unable to find a statistically significant association between the (s) allele carrier status and an increased risk for the use of any psychotropic agents in our study sample.

CHAPTER 08. SUMMARY AND CONCLUSIONS

C08 Part 01 Comorbidity: Summary

C08.P01.S01 Comorbidity in General Medicine

Comorbidity has become an important area of study in medicine due to the realization that the management of patients with multiple coexisting conditions has become the norm rather than the exception in most clinical settings. (C2R01-02).

Comorbidity can impact the clinical presentation, the prognosis, and clinical management of those affected. It has a strong impact on mortality, health-related quality of life, and overall daily functioning (C2R03-07). In addition, it is an important factor in the growing costs of medical care (C2R08).

C08.P01.S02. Conceptualization and Classification of Comorbidity

Comorbidity is defined as "any distinct additional clinical entity that has existed or that may occur during the clinical course of a patient who has the index disease under study" (C2R09). Through the years, several different classifications of the phenomenon of comorbidity have been proposed. These classifications focus on the etiological, the temporal, and the hierarchical aspects of the co-occurring conditions under study.

C08.P01.S03. Comorbidity in Mental Health

The concept of comorbidity in mental disorders has been transformed. The use of the term comorbidity in psychiatry has a different implication than in the rest of the medical field. The complexities in the nature of mental disorders and their classification play an important factor in the distinctive challenge that comorbidity poses in the psychiatric field.

The term comorbidity in mental health is used in diverse scenarios: 1) when a clinical mental disorder (e.g. major depressive disorder, bipolar disorder, schizophrenia) co-occurs with a "physical" or "medical disorder", 2) when a clinical mental disorder co-occurs with a substance abuse disorder, 3) when a clinical mental disorder co-occurs with a personality disorder, and, 4) when two clinical mental disorders co-occur in an individual.

Not all these categories should be considered in the same light. The study of the comorbidity between mental and "physical" or "medical" disorders is an area of interest in its own right. It is the focus of the field of psychosomatics; the study of the relationship between body and mind.

The comorbidity between a clinical disorder and a substance abuse disorder or a personality disorder is an indicator of the heterogeneity of the concept of mental illness in our current classification. In order to increase coverage, our current classification has included different paradigms of mental disorders. These paradigms or concepts act as different viewpoints from where to diagnose a subject. An individual can be diagnosed with a substance abuse disorder, a personality disorder, and, additionally with a clinical disorder. These three diagnoses can be seen as three different mental disorders or complementary perspectives from where to label the manifestations of a single condition.

In contrast, the co-occurrence of two "clinical conditions" can present a challenge to the basic tenets of our current classification of mental disorders. The Diagnostic and Statistical Manual of Mental Disorders (C2R12), introduced a categorical diagnoses model for major

mental disorders. The categorical model purports that each clinical syndrome should be validated by its clear separation from other disorders, a particular clinical course as well as a specific genetic aggregation found in family studies. Thus, a high degree of comorbidity between mental disorders is contradictory to a paradigm that proposes a clear distinction between disorders.

C08.P01.S04. Prevalence of Comorbidity between Mental Disorders in Epidemiologic Studies

Large-scale epidemiologic surveys have determined a high degree of comorbidity between mental and substance use disorders. The Epidemiologic Catchment Area Program (ECA) (C2R25, 26, 27, 28) investigators reported that 60% of those diagnosed with a mental disorder, had at least one additional condition. The National Comorbidity Study (NCS) (C2R29), showed similar results in a national based sample. The lifetime prevalence for any psychiatric or substance abuse disorder for adults was 48%. Stratifying the subjects by the number of lifetime prevalence diagnoses received, 21.0% of the sample met criteria for only 1 disorder, 13.0% of the sample met criteria for only two disorders, and the remaining 14.0% of the sample met criteria for three or more disorders in their lifetime. When examining the total number of diagnoses by subject, 20.6% of the disorders were diagnosed in subjects that met criteria for only one psychiatric disorder, 25.5% of the disorders originated in subjects that were diagnosed with two psychiatric disorders, and, finally 53.9% of the lifetime disorders diagnosed in a sample were diagnosed in subjects that met criteria for three or more lifetime disorders.

C08.P01.S05. Comorbidity of Anxiety and Depressive Disorders

Results from the National Comorbidity Study revealed that only 26% of the subjects with Major Depressive Disorder (MDD) had this condition as sole or "pure" disorder. This meant that

74% of all NCS respondents with a lifetime history of MDD had an additional psychiatric condition (C2R29). In the National Comorbidity Survey Replication (NCS-R) (C2R40), the majority of respondents (72.1%) with lifetime MDD reported at least one other lifetime DSM-IV disorder. Of the respondents with lifetime MDD, 59.2% also met criteria for lifetime anxiety disorder, 24.0% met criteria for a substance use disorder, and 30.0% met criteria for an impulse control disorder (C2R40).

C08. Part 02. Serotonin Transporter Gene: Summary

C08.P02.S01. Serotonin and Serotonin Transporter

Serotonin plays a regulatory function in the central nervous system (C3R05). The serotoninergic system can reduce or increase anxiety and impulsivity, either directly or by altering functions of other neurotransmitter systems (C3R06). In addition, serotonin modulates arousal and prevents uncontrolled anxiety or panic through its effect on the locus coeruleus (C3R07).

The serotonin transporter (SERT) is a pre-synaptic plasma membrane transporter. The SERT modulates the serotonergic neurotransmission by regulating the magnitude and duration of serotonergic responses. It has been established that both the tricyclic antidepressants (TCAs) as well as the newest serotonin reuptake inhibitors (SRIs) exert their initial pharmacological effect by binding to the SERT. The blockade of the SERT function increases the levels of serotonin in the synaptic cleft. This increase in serotonin promotes secondary changes in the serotoninergic transmission both at the presynaptic and postsynaptic levels that are posited as the mechanism of action for both the TCAs and SRIs (C3R05, C3R13).

C08.P02.S02. The Serotonin Transporter Gene Polymorphism and Its Association with Psychopathology

The human serotonin transporter (SERT) is encoded by a single gene (SLC6A4) located on the long arm of chromosome 17 (17q111-17q12). The most investigated area of the SLC6A4 is the serotonin transporter gene promoter region (5-HTTLPR). The 5-HTTLPR has been the object of great attention due to a functioning polymorphism. This polymorphism is constituted by a 44 base pair deletion /insertion in the 5' regulatory region. The polymorphic variant that includes this 44 base pair is referred as the long (L) allele, the variant without the 44 base pair is also called the short (S) allele (C3R14, C3R15).

The decreased level of transcriptional efficacy of the SERT by the short (S) allele has been associated with several psychiatric conditions (C3R16, C3R17), in particular depression, as well as suicidal behavior, and response to antidepressant treatment. There is a copious body of literature on the SERT polymorphism and its potential association with diverse psychiatric conditions. The results of these investigations, have been, so far, inconclusive.

Chapter 08 Part 03: SERT Polymorphism and Psychopathology. Highlights of Study Findings

C08.P03.S01. Aims and Participant Selection

We examined the lifetime prevalence (LP) of Alcohol Dependence, Alcohol Abuse, Opioid Dependence, Schizophrenia and other Psychotic Disorders, Major Depressive Disorders (MDD), Bipolar Disorder, Panic Disorder, Agoraphobia, Social Phobia, Obsessive Compulsive Disorder (OCD) , Generalized Anxiety Disorder (GAD), Simple Phobia, Dysthymic Disorder, Anxiety

Disorder Not Otherwise Specified, Depressive Disorder Not Otherwise Specified, and Adjustment Disorder with Depressed Mood in a community-based sample.

Our study sample was the result of a three-phase selection process. The first phase involved the development of the original cohort for the Baltimore site of the Epidemiological Catchment Area (ECA) in the early 1980's (C4R01). The second phase consisted of the follow-up or re-assessment of the sample obtained in the first phase in the Baltimore Epidemiologic Catchment Area Follow up (EFU) in the early 1990's (C4R02- C4R04). The third phase entailed the development of a sub-sample of the EFU. This third re-assessment was the source of our study sample (C4R06- C4R07).

Our study participants were assessed by a psychiatrist using the Schedule for Clinical Assessment in Neuropsychiatry (SCAN) (C4R08-09) (N=847). In addition, the majority of participants provided a sample for genetic testing (N=628).

C08.P03.S12. Lifetime Prevalence and Comorbidity in the Whole Sample

The disorders with the highest lifetime prevalence were Alcohol Dependence (20.90 (95% CI: 18.32; 23.82), followed by Major Depressive Disorder (MDD) (17.95 (95% CI: 15.54; 20.73), Simple Phobia (12.51 (95% CI: 10.47; 14.95)), and Social Phobia (11.81 (95% CI: 9.82; 14.91), respectively.

There was a significant and extensive comorbidity between anxiety disorders, mood disorders, and Alcohol Dependence. Agoraphobia, Social Phobia, Obsessive Compulsive Disorder (OCD), Generalized Anxiety Disorder (GAD), and Simple Phobia were highly comorbid with each other and with mood disorders. The odds of having a lifetime prevalence diagnoses of Panic Disorder is 5.51 times higher in subjects that have a lifetime diagnoses of Social Phobia than in those who did not receive this diagnosis. The odds of receiving a diagnoses of OCD

during their lifetime is 7.96 times higher in subjects who have received a diagnosis of Social Phobia than in subjects who did not receive this diagnosis. MDD was significantly comorbid with the majority of the anxiety disorders: namely with Panic Disorder (OR: 3.20), Agoraphobia (OR: 2.79), Social Phobia (OR: 2.46), and, OCD (OR: 4.74). Bipolar Disorder was highly comorbid most anxiety disorders: namely, with Panic Disorder (OR: 4.14), Agoraphobia (OR: 3.76), Social Phobia (OR: 2.46), OCD (OR: 4.76) and, GAD (OR: 3.19). Finally Alcohol Dependence was highly comorbid with MDD (OR: 1.52), and Bipolar Disorder (OR: 2.71)

C08.P03.S03. Lifetime Prevalence of Selected Disorders and its Association with SERT Polymorphism

We examined the association of the lifetime prevalence of the 16 disorders included in this investigation and the SERT polymorphism using Poisson Regression models. Panic Disorder was the only condition in which the carriers of the short (S) allele of the SERT polymorphism had an increased risk for receiving a lifetime prevalence diagnoses (2.61 (95% CI: 1.20; 5.69), p=0.02). No evidence of a gender-specific effect was detected when the analysis was stratified by sex. This association of the SERT polymorphism and Panic Disorder was significant adjusted for ethnicity.

C08.P03.S04. Comorbidity between Selected Disorders and its Association with SERT Polymorphism

Using logistic regression models, we examined the odds of comorbidity between all the included psychiatric conditions. We can posit that two patterns of correlations or comorbidities between the individual mental disorders emerge. Anxiety Disorders are highly comorbid with each other, and with MDD and Bipolar Disorder, as well as with Alcohol Dependence. In

addition, Major Depressive Disorder and Bipolar Disorder had a high degree of comorbidity with Alcohol Dependence. These findings were in agreement with previous reports of large scale epidemiologic studies above mentioned.

We examined the association between the (s) allele carrier status and the odds of being diagnosed a given comorbidity. The SERT (s) allele carrier status was associated with a significant increase in the odds for comorbidity in three dyads. For subjects diagnosed with Major Depressive Disorder, the carriers of the (s) allele, had a risk for being diagnosed with Social Phobia that was 5.13 times higher than the one of the non-carriers (OR: 5.13 (95%CI: 1.79; 14.74)). For subjects diagnosed with Agoraphobia, the carriers of the (s) allele, had a risk for being diagnosed with Major Depressive Disorder that was 4.69 times higher than the one of the non-carriers (OR: 4.69 (95%CI: 1.11; 19.83). Finally, for subjects diagnosed with Social Phobia, the carriers of the (s) allele, had a risk for being diagnosed with Major Depressive Disorder that was 4.8 times higher than the one of the non-carriers (Odds Ratio = 4.80 (95%CI: 1.55; 14.84)).

C08.P03.S05. SERT Polymorphism and Overall Burden for Psychopathology

We later examined the association of the SERT (s) allele carrier status with the prevalence of mental disorders, considered globally. We examined the effect of the (S) allele carrier status in the overall number of lifetime diagnoses. There were no significant differences in the distribution of the number of lifetime diagnoses between the (s) allele carrier and the non-carriers. In addition, the carrier status was not associated with an increase in the odds of being diagnosed with one, or two or more mental disorders as compared to the non-carrier status: namely, the carrier status appeared to have no association with a higher morbidity burden for mental disorders.

Chapter 08 Part 04: Summary on Methodological Issues in the Measurement of Comorbidity Methodological

C08.P04.S01. Aims and Rationale

In Chapter 06 we evaluated the diagnostic and comorbidity patterns of our study sample. Our goal was to measure the comorbidity burden of the individual mental disorders and the cumulative effect of all diagnoses in the whole sample. In order to achieve a quantitative analysis and not a mere description of the phenomenon, we developed indicators based on simple statistical principles. These simple indicators helped us to measure the comorbidity burden relying solely on the observed variables of the sample.

C08.P04.S02. Methodological Approaches

We used three complementary approaches in our analyses of the comorbidity burden of the sample. In the first approach, we measured the weight of the comorbidity of each individual disorder by calculating the ration between tally of the comorbidities and the tally of diagnoses for each diagnoses and for the whole sample. In the second approach, we investigated the impact of different comorbidity pairs or dyads on the whole sample as well as on each of its member disorders. In the third approach, we examined the association between the prevalence of each individual mental disorder and the presence of multiple diagnoses among individuals in the study sample.

C08.P04.S03. First Approach: Comorbidity to Diagnosis Inflation Ratio (CDIR)

In the first analytic approach, we crafted a number of tables for purposes of describing the number of diagnoses and comorbidities in our study population. We calculated a simple ratio between the total number of comorbidities and the total number of diagnoses for each disorder, as well as for the total sample. We named this crude measure the Comorbidity to Diagnosis Inflation Ratio (CDIR). By standardizing the DCIR with the total value, we were able to detect the differential comorbidity burden of each disorder. The CDIR of the whole sample represents the quotient between the Total Number of Comorbidities (n=1,146) and the Total Number of Diagnoses (or Subjects Diagnosed) (n=868) which yielded a value of 1.32 in our population. This means that, in our sample, there was an average of 132 comorbidities per 100 diagnoses. This measure allowed us to detect those conditions with the highest comorbidity burden in the sample. OCD was the psychiatric condition with the highest comorbidity burden which had a CDIR of 2.5. This translates into the presence of 2.5 comorbidities for each OCD diagnosis. The SCDIR for OCD yielded a value of 1.89. This estimate indicates that OCD has a comorbidity burden that is 89% higher than the one observed in the overall sample. Following OCD, in order of decreasing burden, there are three anxiety disorders, Agoraphobia: CDIR = 2.12 and SCDIR= 1.61; Social Phobia: CDIR=1.65 and SCDIR=1.25; and Panic Disorder: CDIR= 1.61 and SCDIR= 1.22.

C08.P04.S04. Second Approach: Impact of the Comorbidity Dyads

In the second analytic approach, we examined the impact of each comorbidity pair or dyad on the whole sample, and on each of its integrating or member conditions. In order to

obtain a quick summary measure of the impact of every comorbidity dyad on both its integrating condition, we calculated a ratio of probabilities. We labeled this indicator as the Ratio of Conditional to Marginal Probabilities (RCMP). This ratio has several appealing statistical characteristics and it is relatively easy to compute for all conditions. This ratio can also be expressed as the conditional probability of Condition A given Condition B divided by the probability of Condition A (PA/B / PA or PB/A /PB). In addition, this indicator can also be expressed as the observed prevalence of the comorbidity pair divided by its expected prevalence. A value of 1.0 indicates that Conditions A and B are independent. A value of less than one indicates a negative tendency towards comorbidity whereas a value of greater than 1 indicates that the observed comorbidity exceeds the expected frequency. Panic Disorder, Agoraphobia, Social Phobia, Obsessive Compulsive Disorder, and Generalized Anxiety Disorder were the conditions that have both the highest number of comorbidities and the highest value for both the RCMPs and the Odds Ratios (Table C6T02). These conditions were comorbid with each other as well as with other disorders with a high prevalence (e.g., Major Depressive Disorder, Social Phobia, and Alcohol Dependence).

C08.P04.S05. Third Approach: Stratification, Adjustment and Diagnostic Inflation Ratio

In the last analytic approach, we stratified individuals in the study sample according to the number of diagnoses received (0, 1, 2 or more conditions). Tables C6T03A and C6T03B displayed the frequency of each diagnostic strata and the prevalence of each condition within each diagnostic strata. The stratification of diagnoses by diagnostic group or strata, helped us to understand that comorbidity creates a scenario of over-representation of individuals with multiple diagnoses. Our findings suggest that our sample was ruled by a 70/30 ratio, in which

70% of the individuals in the sample contributed only with 30% of the diagnostic information. In order to measure this over-representation of individuals with multiple diagnoses, we adjusted all diagnostic and comorbidity information to be identical to the number of individuals diagnosed. (Table C6T03C). We called this indicator the Diagnostic Inflation Ratio (DIR). In the entire study sample, the DIR corresponds to the quotient of the Total Number of Diagnoses (N=868) with the Total Number of Individuals Diagnosed (N=492). In probability terms, the DIR is the expected value of diagnoses that we will find in a subject from the sample picked at random. For the whole sample the DIR yielded a value of 1.76. The DIR can provide a quantitative indicator of the comorbidity burden of the sample that could be compared with values obtained from other samples, as well as between disorders within the sample. The DIR of OCD indicates that we can expect to find 2.82 diagnoses from any individual of the sample affected with OCD, picked up at random. In addition, we also analyzed the ratio of the Total Number of Comorbidities (N=1,146) to the Total Number of Individuals Diagnosed (N=492). For consistency reasons, we labeled this measure as the Comorbidity Inflation Ratio (CIR). The CIR for the whole sample was 2.33 which means that we can expect to find 2.3 comorbidities in an individual of the sample picked at random (of the individuals that have received one diagnosis at least). We later normalized the DIR and CIR of the individual disorders with the DIR and CIR of the total sample to be able to compare the individual disorders (Table C6T03C). These findings were consistent with previous measures. The anxiety disorders were the conditions with the highest values for all indicators. Specifically, Panic Disorder (DIR: 2.07, SDIR: 1.18, CIR: 3.36, SCIR: 1.43), Agoraphobia (DIR: 2.45, SDIR: 1.39, CIR: 5.20, SCIR: 2.30), Social Phobia (DIR: 2.11, SDIR: 1.19, DIR: 3.47, SCIR: 1.49), Obsessive Compulsive Disorder (DIR: 2.82, SDIR: 1.60, CIR: 7.05, SCIR: 3.02) and Generalized Anxiety Disorder (DIR: 1.99, SDIR: 1.128, CIR: 3.50, SCIR: 1.50) were the individual conditions whose comorbidity burden largely outweighed both the rest of the disorders and the average burden for the whole sample.

C08.P04.S06. Relationship between Individuals, Diagnoses, and Comorbidities in a Sample

Finally, we analyzed the association between the Total Number of Individuals Diagnosed, the Total Number of Diagnoses, and the Total Number of Comorbidities in the sample. We concluded that these can be seen as 3 related random probability distributions that share random elements, but have unique fixed features. The random elements depend exclusively on the sample to be analyzed and include: 1) the number of diagnostic groups or strata (that can be seen in probability terms as the number of possible outcomes), and 2) the number of individuals in each diagnostic strata, that in probability terms translates into the probability of each outcome (as a proportion in relation to the total number).

The fixed elements were the value attached to each outcome were unique to each distribution, and did not change when different samples were analyzed. The value attached for each outcome for the distribution of Total Number of Individuals was 1 for all outcomes. The value for each outcome for the distribution of the Total Number of Diagnoses was the modal diagnoses (MD) of each diagnostic group or strata. Finally, the value attached to each outcome for the Total Number of Comorbidities was equal to the product of the modal diagnoses of the diagnostic strata multiplied by itself minus one (MD x MD-1). We could see that the value of the mean or expected value of the distribution of the Total Number of Diagnoses was the DIR, the mean or expected value of the Total Number of Comorbidities was the CIR, and the ratio between the CIR and DIR was the CDIR.

Chapter 08 Part 05: Summary on Analysis of Time Achieve Criteria for Full Diagnosis and Its Association with the Serotonin Transporter Gene Polymorphism

C08.P05.S01. Time to Diagnosis, Aims and Introduction

We examined the differences in the recorded time that the affected subjects required to achieve full criteria for the selected diagnoses, and the association of this time to diagnosis with the Serotonin Transporter Gene (SERT) Polymorphism

In order to achieve this goal, we used several statistical techniques to examine the "time to event" variable. By using these statistical techniques that focus on the time to event, in this case time to diagnosis, we aimed at correcting the limitation of the previous analyses that ignored the differences in the time at risk of the participants. .

C08.P05.S02. Findings: Time to Diagnoses and SERT Gene Polymorphism

The SERT (s) allele carrier state was associated with nearly three times higher risk for receiving a diagnosis of Panic Disorder (Incidence Rate Ratio=2.70 (95% CI: 1.13-7.42). For Panic Disorder subjects, this difference between carriers and non-carriers was also observed in the Log-Rank Test, and in the unadjusted Hazard Ratio. The Hazard Ratio, adjusted for gender, ethnicity, and marital status, was of borderline significance (Adjusted Hazard Ratio: 2.35 (95% CI: 1.00-2.51).

Lastly, the SERT (s) allele carrier state was associated with a significant 77% decrease in risk for receiving a diagnosis of Obsessive Compulsive Disorder (Incidence Rate Ratio=0.13 (95%CI: 0.00-0.99). For Obsessive Compulsive Disorder, this difference between carriers and non-carriers was also significant for the Log-Rank Test, and both the unadjusted Hazard Ratio,

as well as for the Hazard Ratio adjusted for gender, ethnicity, and marital status (Adjusted Hazard Ratio: 0.11 (95% CI: 0.01-0.95).

Chapter 08 Part 06: Summary: Use of Psychotropic Agents and Its Association with the Serotonin Transporter Gene Polymorphism

C08.P06.S01. Aims and Rationale for the Analysis of Use of Medications

We examined the use of psychotropic medications in our study participants and its association with the SERT Gene Polymorphism.

Several studies (C3R48-50) have reported that subjects who were homozygotes for the (L) SERT polymorphism, had significantly better antidepressant responses than subjects who were carriers of the (S) allele.

C08.P06.S02. Analysis of Use of Medications Findings

Antidepressant agents were the most widely prescribed for our subjects (8.85 per 100 subjects), followed by anti-anxiety agents (4.25 per 100 subjects). The overall use of psychotropic agents in the sample (including all types of psychotropic agents) was equal to 10.51 per 100 subjects. The use of psychotropic agents was similar for both the SERT (s) allele carrier and the (s) allele non-carrier participants.

Chapter 08 Part 07: Concluding Remarks

C08.Part 07.S01. Introduction

We can divide our work into three interrelated goals. The first goal was to examine the lifetime prevalence and comorbidity of selected mental disorders in a community-based sample. The second goal was to examine the association of the SERT gene polymorphism with and the prevalence, comorbidity burden, and, treatment patterns of the most frequently diagnosed mental disorders in a group of 847subjects that were sampled from the Epidemiologic Catchment Area (ECA) in Baltimore, Maryland: namely, whether the subjects who were carriers of the short (s) allele of the SERT gene had an increase rate of morbidity and comorbidity for mental disorders. The final and third goal, born out of the need to fulfill the first two goals, was to develop instruments to quantitatively and comprehensively measure the comorbidity burden in a sample.

C08.Part 07.S01. Lifetime Prevalence and Comorbidity of Selected Mental Disorders in a Community Based Sample.

Our findings on the prevalence and comorbidity are consistent to the cited literature. We found extensive comorbidity between the major mental disorders. In particular between anxiety disorders, mood disorders, and Alcohol Dependence. Agoraphobia, Social Phobia, Obsessive Compulsive Disorder (OCD), Generalized Anxiety Disorder (GAD) were highly comorbid. This is consistent with literature y (C2R43). Comorbidity between anxiety disorders and MDD was

significant between most of the anxiety disorders: namely with Panic Disorder (OR: 3.20), Agoraphobia (OR: 2.79), Social Phobia (OR: 2.46), and, OCD (OR: 4.74). These findings are consistent with the previously cited results of large community based studies as the National Comorbidity Survey. Our proposed instruments can prove to be useful in this area, as they can provide a quantitative indicator of the comorbidity burden of each individual disorder. The DIR and CIR can be used as a single measure of the comorbidity of each condition. This widespread and significant comorbidity burden between could be an indicator of the limitations in the validity of the categorical psychiatric classification. Categorical diagnoses can be great tools for communication in clinical settings, and be useful in research. Thus, a high degree of comorbidity between categorical diagnoses can create communication barriers between providers and patients, and unwanted bias for research, due to misclassification of individuals

Considering the relationship between diagnoses and individuals diagnosed, our findings indicate that comorbidity entails a pattern of under-representation of a majority of the individuals in the sample. The participants that have been diagnosed with only one condition is equivalent to 51.83% of the total individuals of the sample that have received a psychiatric diagnosis. Paradoxically, this group only represents 29.38 % of the total diagnoses present in the sample: namely, over 70% of the diagnoses in the sample originated from individuals with more than one diagnoses. Thus, our findings are nearly identical to those reported by the NCS investigators. Kessler et al. reported that 56.25% of all the NCS participants that received a DSM diagnoses met criteria for more than one disorder, and, in addition 79.4% of the lifetime diagnoses of psychiatric and substance abuse disorders diagnosed in the NCS sample were comorbid conditions (C2R29).

In summary, in our relatively small sample of participants interviewed by psychiatrists using the SCAN, we were able to see a widespread comorbidity burden amongst mental

disorders similar to the large scale epidemiologic studies that relied on non-psychiatrists or diagnostic purposes.

C08.Part 07.S02. Findings SERT Gene Polymorphism and Psychopathology

We found an increased lifetime prevalence of Panic Disorder in the study participants who were carriers of the (s) alleles. Our findings are in agreement with previous literature that reports an increase in anxiety-related traits in the carriers of the (s) allele of the SERT promoter region polymorphism (C3R15, C3R24). However, the findings on the association between the 5-HTTLPR and Panic Disorder have been inconsistent. In our Poisson models, the lifetime prevalence remained significant after adjustment for gender and race. In the time- to –event analysis, the controlling for gender and race, the association was only of borderline significance.

We found a significant association between SERT (s) allele carrier status and a decreased risk to be diagnosed with Obsessive-Compulsive Disorder in the time-to-event analysis. After controlling for gender and race, this association remained significant. This finding is consistent with previous studies (C3R63, C3R54), that reported an association between the long (l) allele of the SERT promoter region with OCD. Thus, the (s) carrier status could have a "protective" effect for OCD.

In addition, the carriers of the (s) allele had a significant increased risk for two comorbidity pairs, MDD and Social Phobia, and Agoraphobia and MDD in logistic regression models. Due to the limited number of affected individuals in each comorbidity dyad, we were unable to adjust for gender and race.

When comparing the overall number of diagnoses, there was no sign of increase in the burden for psychopathology in the carriers of the (s) allele

In summary, our findings suggest a limited effect of the SERT promoter gene polymorphism in the overall psychopathology burden. It is important to highlight the limitation of our small sample size. We have also considered the SERT promoter region polymorphism in a bi-allelic approach. We were unable to explore a more novel tri-allelic approach for the 5-HTTLPR, as well as additional single nucleotide polymorphisms present in the SERT gene, due to availability and limited sample size.

In addition, we should acknowledge the limitation of a sample that originates in only one geographical region, and has a multi-ethnic composition. This could have introduced population stratification bias in our findings.

Nevertheless, considering the role of serotonin transmission in the central nervous system, and the role of the SERT in the regulation of serotonin transmission, the existence of a polymorphism in the gene that codes the SERT should continue to be an area of active interest in research. Especially if this polymorphism impacts on the SERT function, and therefore, on the serotonin transmission. Future work should combine large population based cohorts, nation-wide sampled. This future cohorts could be comprehensively screened for psychopathology using standardized instruments, and genotyped for all possible functional variants of the SERT gene

C08.Part 07.S03. Utility of Instruments and Adjustment Methods

We believe that the proposed measures might be helpful instruments in the measurement and characterization of the diagnostic and comorbidity patterns in a sample. They are easy to instrument, and can provide a comprehensive and novel analysis of the relationship between individuals diagnosed, diagnoses, and comorbidities.

At present, we believe that the medical field is struggling with the phenomenon of comorbidity or multi-morbidity. There is a growing awareness of the increased cost and clinical effects that comorbidity can have on the diagnosis and treatment of the population. Thus, simple methods to quantify this phenomenon can provide some help in this endeavor.

These methods can be used to compare the different samples, or different subgroups in the single sample as we have done in comparing the carriers of the SERT (s) allele with the non-carriers in our study sample in the Appendix 02.

In addition, the proposed instruments can be useful in the quantification and characterization of the different diagnoses contained in the sample, as they are able to quantify and compare the comorbidity burden of each individual diagnosis contained in the sample

These indicators are based on simple mathematical principles, rely on counting subjects characteristics. They can therefore be used for other purposes such as pharmaco-epidemiology. In this case, we will be counting number of pharmaceutical prescribed and measuring the burden or degree of polypharmacy use in a cohort or service dataset.

In addition, these indicators could provide an individual measure of comorbidity for a single individual in a cohort, and can be combined with univariate and multivariate methods. They could be used in clinical settings, research, and health-services research.

Comorbidity in mental health has the added effect of a challenge to the validity of the diagnostic classification of mental disorders. We hope that our proposed instruments can be useful in the complex enterprise of refining our nosology.

In summary, these indicators are quick to implement. They are based on clear mathematical principles. They can provide a descriptive and analytic measure of the diagnostic and comorbidity pattern in a sample.

CHAPTER 04: TABLES

Table C4AT01. Demographic Characteristics: Whole and Genotyped Samples.

	Description	*Whole Sample (n=816)*	*Genotyped (n=602)*	*Non-Genotyped (n=214)*	*Significance (Gen/ Non-Gen)*
Age in Years	*Mean (95% CI)*	*48.29 (47.35;49.23)*	*47.19(46.18; 48.20)*	*51.37 (49.23; 53.52)*	*<0.001.*
Gender N (%)	*Females*	*522 (63.97%)*	*381 (63.29%)*	*141 (65.89%)*	*0.5*
	Males	*294 (36.03%)*	*221 (36.71%)*	*73 (34.11%)*	
Race N (%)	*White*	*489 (59.93%)*	*362 (60.13%)*	*127 (59.35%)*	*0.84*
	Non-Whites	*327 (40.07%)*	*240 (39.87%)*	*87 (40.65%)*	
*High School Diploma N (%) *N=588*	*No High School*	*289 (49.15%)*	*210 (48.39%)*	*79 (51.30%)*	*0.83*
	High School	*255 (43.47%)*	*191 (44.01%)*	*64 (41.56%)*	
	GED	*44 (7.48%)*	*33 (7.60%)*	*11 (7.14%)*	
Highest Educational Level Achieved N (%)	*HS Incomplete*	*317 (38.85%)*	*231 (38.37%)*	*86 (40.19%)*	*0.92*
	HS Complete	*271 (33.21%)*	*203 (33.72%)*	*68 (31.78%)*	
	College Incomplete	*143 (17.52%)*	*104 (17.28%)*	*39 (18.22%)*	
	College Complete	*85 (10.42%)*	*64 (10.63%):*	*21 (9.81%)*	
Marital Status N (%)	*Married*	*340 (41.67%)*	*261 (43.36%)*	*79 (36.92%)*	*0.10*

Table C4AT01 displays the demographic characteristics of both genotyped (N=816 that had available demographic information out of the whole sample of N=847), and non-genotyped subjects (N=628).

Table C4AT02. Genotypes Distribution of Serotonin Transporter Gene

	Frequency	*Whole Sample (%)*	*Genotyped Sample (%)*
1=L/L	*280*	*33.1*	*44.6*
2=L/S	*274*	*32.3*	*43.6*
3=S/S	*74*	*8.7*	*11.8*
Total Genotyped	*628*	*74.1*	*100.0*
Non-Genotyped	*219*	*25.9*	
Total Sample	*847*	*100.0*	

Table C4AT02 summarizes the genotypes distribution of the genotyped sub-sample (N=628)

CHAPTER 05: TABLES

Table C5T01. Lifetime Prevalence Estimates as Percentages, for the Whole Sample, the Genotyped Sample, and by SERT (S) Carrier Status

Row		Whole Sample (n=847)	Genotyped Sample (n=628)	SERT Carrier (ss+sl) (n=348)	SERT Non-Carrier (ll) (n=280)	Carrier/ Non-Carrier	Sig
01	Alcohol Dependence	20.90 (18.32; 23.82)	20.22 (17.3; 23.622)	20.98 (17.11; 25.72)	19.29 (15.18; 24.51)	1.09 (0.79; 1.49)	0.60
02	Alcohol Abuse	5.67 (4.31; 7.46)	6.37(4.72; 8.60)	6.61 (4.45; 9.81)	6.07(3.83; 9.62)	1.09 (0.59; 2.00)	0.78
03	Major Depressive Disorder	17.95 (15.54; 20.73)	18.79 (15.97;22.11)	18.39 (14.74;22.95)	19.29 (15.18; 24.51)	0.95 (0.69;1.32)	0.78
04	Bipolar Disorder	2.6 (1.72; 3.92)	2.39 (1.45; 3.94)	3.16 (1.77; 5.65)	1.43 (0.54; 3.78)	2.21 (0.71; 6.87)	0.17
05	Psychotic Disorders	1.42 (0.81; 2.48)	0.96 (0.43; 2.12)	0.86 (0.28; 2.66)	1.07 (0.035; 3.30)	0.80 (0.16;3.96)	0.79
06	Panic Disorder	5.43 (4.10; 7.19)	5.41 (3.90; 7.51)	7.47 (5.16; 10.81)	2.86 (1.44; 5.66)	2.61 (1.20; 5.69)	0.02*
07	Agoraphobia	5.90 (4.51; 7.72)	5.94 (3.50; 10.06)	5.17(3.30; 8.11)	6.79 (4.40; 10.47)	0.76 (0.41; 1.42)	0.40
08	Social Phobia	11.81 (9.82; 14.19)	11.62 (9.37; 14.42)	12.64 (9.59; 16.67)	10.36 (7.34; 14.62)	1.22 (0.78; 1.90)	0.38
09	Obsessive Compulsive Disorder	1.65 (0.98; 2.78)	1.27 (0.64; 2.54)	1.15 (0.43; 3.05)	1.43 (0.54; 3.78)	0.80 (0.20; 3.24)	0.76
10	Generalized Anxiety Disorder	2.95 (2.01; 4.34)	2.87 (1.82; 4.52)	2.30 (1.16; 4.56)	3.57 (1.94; 6.56)	0.64 (0.26; 1.61)	0.35
11	Anxiety Disorder NOS	2.48 (1.63; 3.78)	2.07 (1.21; 3.54)	2.01 (0.97; 4.19)	2.14 (0.97; 4.73)	0.94 (0.32; 2.76)	0.91
12	Dysthymic Disorder	1.06 (0.55; 2.04)	1.27 (0.64; 2.54)	1.15 (0.43; 3.05)	1.43 (0.54; 3.78)	0.80 (0.20; 3.24)	0.76
13	Depressive Disorder NOS	2.13 (1.35; 3.36)	2.23 (1.33; 3.74)	2.01 (0.97; 4.19)	2.50 (1.20; 5.20)	0.80 (0.29; 2.27)	0.68
14	Simple Phobia Disorder	12.51 (10.47; 14.95)	14.17 (11.69; 17.18)	12.64 (9.59; 16.67)	16.07 (12.30; 21.00)	0.79 (0.54; 1.16)	0.22
15	Adjust DO Depressed Mood	3.78 (2.69; 5.31)	3.98 (2.71;5.85)	4.02 (2.41;6.72)	3.93 (2.20;7.01)	1.02 (0.47;2.22)	0.95
16	Opioid Dependence	4.25 (3.09; 5.85)	3.98 (2.71;5.85)	4.02 (2.41;6.72)	3.93 (2.20;7.01)	1.02 (0.47;2.22)	0.95
	Column	01	02	03	04	05	06

Table C5T01 displays the un-weighted LP prevalence estimates as percentages with 95% confidence intervals (CI) of the 16 Axis I disorders examined in a subsample. Column 01 summarizes the un-weighted LP estimates for the whole sample (N=847). Column 02 displays the un-weighted LP estimates for the genotyped sub-sample (N=628). Column 03 displays the un-weighted LP estimates for the SERT (s) allele carrier sub-sample (N=348). Column 04 displays the un-weighted LP estimates for the SERT (s) allele non-carrier sub-sample (N=280). Column 05 displays the prevalence ratio estimates between the carrier and the non-carrier subsamples with 95% Confidence Intervals. Column 06 summarizes the p-values for the prevalence ratio estimates of column 05. SERT (s) allele carrier status was associated with an increase in risk for Panic Disorder. Carriers of the SERT (s) allele had a 2.61 higher risk for a LP diagnosis of Panic Disorder (Prevalence Rate Ratio: 2.61 (95% CI: 1.20; 5.69) p: 0.02)

Table C5T02. Lifetime Prevalence for Panic Disorder as Percentages (95% CI) by SERT (S) Carrier Status. Stratified by Gender

Row		Gender	Carrier 5HTT (ss+sl) % (n=348)	Non Carrier 5HTT (ll)% (n=280)	Prevalence Rate Ratio Carrier/ Non-Carrier	Sig
01	Panic Disorder	Females	11.17 (7.60; 16.41)	4.00 (1.95; 8.27)	2.79 (1.23; 6.36)	0.01
02		Males	23.08 (0.75; 7.06)	10.99 (0.16; 7.72)	2.1 (0.22; 19.87)	0.52
	Column	01	02	03	04	05

Table C5T02 displays the un-weighted LP prevalence estimates with 95% confidence intervals (CI) for Panic Disorder, stratified by gender. Column 02 displays the un-weighted LP estimates for Panic Disorder in males and females who are SERT (s) allele carriers (N=348). Column 03 displays the un-weighted LP estimates for Panic Disorder in males and females who are non-carriers (N=280). Column 04 displays the prevalence ratio estimates between the carrier and the non-carrier subsamples with 95% Confidence Intervals for each gender. Column 04 summarizes the p-values for the prevalence ratio estimates of column 04.

Table C5T03. Tetrachoric Correlations 16 Axis I Psychiatric Disorders Lifetime Prevalence Whole Sample (N=847)

Row		Alcohol Dep	Alcohol Abuse	Major Depr DO	Bipolar Disorder	Psychotic Disorders	Panic Disorder	Agora phobia	Social Phobia	OCD	Gen Anx DO	Anxiety DO NOS	Dysthymic Disorder	Depressive DO NOS	Simple Phobia	Adjust DO Dep Mood	Opioid Dep
01	Alcohol Dependence	1.0000															
02	Alcohol Abuse		1.0000														
03	Major Depressive Disorder	0.1378		1.0000													
04	Bipolar Disorder	0.2526		-1.0000	1.0000												
05	Psychotic Disorders					1.0000											
06	Panic Disorder			0.3228	0.3174		1.0000										
07	Agoraphobia	0.3097		0.2872	0.2973		0.3744	1.0000									
08	Social Phobia	0.1745		0.2777	0.2575		0.2436	0.4564	1.0000								
09	Obsessive Compulsive Disorder			0.3686	0.3805			0.4192	0.4763	1.0000							
10	Generalized Anxiety Disorder			0.2965					0.3252		1.0000						
11	Anxiety Disorder NOS											1.0000					
12	Dysthymic Disorder										0.4531		1.0000				
13	Depressive Disorder NOS													1.0000			
14	Simple Phobia Disorder							0.2640	0.2989		0.3572				1.0000		
15	Adjust DO Depressed Mood			-0.3783											0.3135	1.0000	
16	Opioid Dependence	0.2852												0.4263			1.0000
	Column	01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16

Table C5T03 summarizes the significant (p-value: < 0.05) tetrachoric correlations between all the 16 mental disorders for the whole study sample (N=847).

Table C5T04. Comorbidity Odds Ratio Lifetime Prevalence All Disorders, Whole Sample (N=847)

Row		Alcohol Dep	Alcohol Abuse	Major Depr DO	Bipolar Disorder	Psychotic Disorders	Panic Disorder	Agora phobia	Social Phobia	OCD	Gen Anx DO	Anxiety DO NOS	Dysthymic Disorder	Depressive DO NOS	Simple Phobia	Adjust DO Dep Mood	Opioid Dep
01	Alcohol Dependence	N/A	0.52	1.52*	2.71*	0.34	0.92	2.98*	1.75*	1.53	1.20	0.62	0.47	1.47	1.12	1.27	2.86*
02	Alcohol Abuse	0.52	N/A	0.91		1.52	2.15	1.07	1.80	2.85				0.98	0.80		0.98
03	Major Depressive Disorder	1.52*	0.91	N/A		1.53	3.20*	2.78*	2.46*	4.74*	3.19*	1.86	2.31	0.57	1.59	0.14	2.09*
04	Bipolar Disorder	2.71*			N/A		4.14*	3.76*	2.92*	6.78*					0.33		
05	Psychotic Disorders	0.34	1.52	1.53		N/A		3.28	1.50			3.70		4.37	2.37		
06	Panic Disorder	0.92	2.15	3.20*	4.14*		N/A	4.51*	2.51*	2.99	1.54			1.02	1.27	1.17	2.29
07	Agoraphobia	2.98*	1.07	2.78*	3.76*	3.28	4.51*	N/A	5.42*	6.84*	3.21*	2.76	2.01	0.94	2.66*	0.50	1.48
08	Social Phobia	1.75*	1.80	2.46*	2.92*	1.50	2.51*	5.42*	N/A	7.96*	3.73*	1.25	2.16	1.51	2.74*	1.07	0.93
09	Obsessive Compulsive Disorder	1.53	2.85	4.74*	6.78*		2.99	6.84*	7.96*	N/A	5.87*		7.93		2.87		
10	Generalized Anxiety Disorder	1.20		3.19*			1.54	3.21*	3.73*	5.87*	N/A		10.12*		4.20*	1.06	
11	Anxiety Disorder NOS	0.62		1.86		3.70		2.76	1.25			N/A		2.38	1.17	2.79	1.13
12	Dysthymic Disorder	0.47		2.31				2.01	2.16	7.93	10.12*		N/A	A	2.02		
13	Depressive Disorder NOS	1.47	0.98	0.57		4.37	1.02	0.94	1.51			2.38		N/A	0.87		7.12*
14	Simple Phobia Disorder	1.12	0.80	1.59	0.33	2.37	1.27	2.66*	2.74*	2.87	4.20*	1.17	2.02	0.87	N/A	3.40*	0.87
15	Adjust DO Depressed Mood	1.27		0.14			1.17	0.50	1.07		1.06	2.79			3.40*	N/A	
16	Opioid Dependence	2.86*	0.98	2.09*			2.29	1.48	0.93			1.13		7.12*	0.87		N/A
	Column	01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16

Table C5T04 displays all the comorbidity odds ratios between the individual mental disorders obtained from logistic regression models for the whole study sample. Empty cells represent comorbidity pairs with insufficient affected individuals in order to complete analysis. The odds ratio with significant results (p-value: < 0.05) are followed by the star sign (*)

Table C5T05. Tetrachoric Correlations 16 Axis I Psychiatric Disorders Lifetime Prevalence, SERT (s) Allele Carriers (SS+ SL) (N = 348)

Row		Alcohol Dep	Alcohol Abuse	Major Depr DO	Bipolar Disorder	Psychotic Disorders	Panic Disorder	Agora phobia	Social Phobia	OCD	Gen Anx DO	Anxiety DO NOS	Dysthymic Disorder	Depressive DO NOS	Simple Phobia	Adjust DO Dep Mood	Opioid Dep
01	Alcohol Dependence	1.0000															
02	Alcohol Abuse		1.0000														
03	Major Depressive Disorder			1.0000													
04	Bipolar Disorder				1.0000												
05	Psychotic Disorders					1.0000											
06	Panic Disorder			0.3810			1.0000										
07	Agoraphobia	0.4565		0.5009			0.4417	1.0000									
08	Social Phobia			0.5511			0.3541	0.4987	1.0000								
09	Obsessive Compulsive Disorder		1.0000							1.0000							
10	Generalized Anxiety Disorder			0.3804					0.4832		1.0000						
11	Anxiety Disorder NOS											1.0000					
12	Dysthymic Disorder												1.0000				
13	Depressive Disorder NOS													1.0000			
14	Simple Phobia Disorder								0.3015						1.0000		
15	Adjust DO Depressed Mood															1.0000	
16	Opioid Dependence													0.5192			1.0000
	Column	01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16

Table C5T05 summarizes the significant (p-value: < 0.05) tetrachoric correlations between all the 16 mental disorders for the SERT (s) Allele Carriers (SS+ SL) (N = 348)

Table C5T06. Tetrachoric Correlations 16 Axis I Psychiatric Disorders Lifetime Prevalence, Non-Carriers Only (LL) (N = 280)

Row		Alcohol Dep	Alcohol Abuse	Major Depr DO	Bipolar Disorder	Psychotic Disorders	Panic Disorder	Agora phobia	Social Phobia	OCD	Gen Anx DO	Anxiety DO NOS	Dysthymic Disorder	Depressive DO NOS	Simple Phobia	Adjust DO Dep Mood	Opioid Dep
01	Alcohol Dependence	1.0000															
02	Alcohol Abuse		1.0000														
03	Major Depressive Disorder	0.3205		1.0000													
04	Bipolar Disorder				1.0000												
05	Psychotic Disorders					1.0000											
06	Panic Disorder			0.5028			1.0000										
07	Agoraphobia				0.5879			1.0000									
08	Social Phobia							0.5669	1.0000								
09	Obsessive Compulsive Disorder							0.6243	0.6677	1.0000							
10	Generalized Anxiety Disorder			0.3947							1.0000						
11	Anxiety Disorder NOS											1.0000					
12	Dysthymic Disorder										0.7113		1.0000				
13	Depressive Disorder NOS													1.0000			
14	Simple Phobia Disorder								0.2965						1.0000		
15	Adjust DO Depressed Mood											0.5854				1.0000	
16	Opioid Dependence																1.0000
	Column	01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16

Table C5T06 summarizes the significant (p-value: < 0.05) tetrachoric correlations between all the 16 mental disorders for the SERT (s) Allele Non-Carriers (LL) (N = 280)

Table C5T07. Association of SERT (s) Carrier Status with Comorbidities, Genotyped Sample (N=628)

Row		Alcohol Dep	Alcohol Abuse	Major Depr DO	Bipolar Disorder	Psychotic Disorders	Panic Disorder	Agora phobia	Social Phobia	OCD	Gen Anx DO	Anxiety DO NOS	Dysthymic Disorder	Depressive DO NOS	Simple Phobia	Adjust DO Dep Mood	Opioid Dep
01	Alcohol Dependence	N/A	1.58	0.72	1.71			3.50	1.04		0.21	0.83		0.22	0.72	2.73	1.48
02	Alcohol Abuse	1.51	N/A	0.48			1.27		1.35						0.24		0.77
03	Major Depressive Disorder	0.61	0.36	N/A			0.44	4.69*	4.80*	1.00	1.00	0.33	3.0		1.30		1.48
04	Bipolar Disorder	3.07			N/A			0.50	0.64								
05	Psychotic Disorders					N/A			0.65								
06	Panic Disorder		3.37	2.03			N/A	3.2	6.22	5.00						0.77	1.67
07	Agoraphobia	1.56		2.31	0.10		0.71	N/A	0.58						0.65		0.77
08	Social Phobia	1.19	1.58	5.13*	0.22	1.00	3.11	1.10	N/A	0.50	4.00			1.00	1.33	1.67	2.73
09	Obsessive Compulsive DO			0.26			0.28		0.15	N/A	*						
10	Generalized Anxiety Disorder	0.17		0.65					1.35		N/A				1.02		
11	Anxiety Disorder NOS	0.74		0.41								N/A			2.10		
12	Dysthymic Disorder			1.71									N/A		1.02		
13	Depressive Disorder NOS	0.24							0.65					N/A			1.67
14	Simple Phobia Disorder	0.50	0.15	1.00				0.62	0.74		1.40	2.00	1.00		N/A	0.70	1.67
15	Adjust DO Depressed Mood	2.27					0.28		1.33						1.03	N/A	
16	Opioid Dependence	1.25	0.73	1.44			0.58	1.06	2.05					2.40	2.10		N/A
	Column	01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16

Table C5T07 Summarizes the ratio of the odds of the SERT (S) allele carriers to the odds of the non-carriers, of the comorbidity for the conditions listed in the row headings, on those subjects who have been diagnosed with the condition listed in the column headings. As an example, for subjects diagnosed with Major Depressive Disorder, the odds of the carriers of the (s) allele for being diagnosed with Social Phobia was 5.13 times higher than the odds of the non-carriers (OR: 5.13 (95%CI: 1.79; 14.74). For subjects diagnosed with Agoraphobia, the carriers of the (s) allele, had a risk for being diagnosed with Major Depressive Disorder that was 4.69 times higher than the one of the non-carriers (OR: 4.69 (95%CI: 1.11; 19.83). For subjects diagnosed with Social Phobia, the carriers of the (s) allele, had a risk for being diagnosed with Major Depressive Disorder that was 4.8 times higher than the one of the non-carriers (Odds Ratio = 4.80 (95%CI: 1.55; 14.84). Please note that order of the conditions matter in the analysis of comorbidity pairs by SERT carrier status (For more information see Tables C5T08 and C5t09)

Table C5T08.Odds Ratio Comorbidity for Social Phobia in SERT S Allele Carriers/ Non-Carriers for Subjects with Major Depressive Disorder

Rows	Grouping	SERT Carrier (ss+sl) Individuals Affected	SERT Non-Carrier (ll) Individuals Affected	Total Number Individuals Affected	Proportion Carriers
01	Comorbid Cases MDD-Social Phobia	22	5	27	0.8148
02	Non- Comorbid Cases MDD	42	49	91	0.4615
03	Totals	64	54	118	0.5424
	Columns	01	02	03	03

Odds Ratio = 5.13 (95%CI: 1.79; 14.74)

Table C5T08 displays the two by two table and analysis for the Odds Ratio for the comorbidity for Social Phobia in subjects with Major Depressive Disorder, in SERT (s) allele carriers vs. non-carriers for in subjects

Table C5T09.Odds Ratio Comorbidity for Major Depressive Disorder in SERT S Allele Carriers/ Non-Carriers for Subjects with Social Phobia

Rows	Grouping	SERT Carrier (ss+sl) Individuals Affected	SERT Non-Carrier (ll) Individuals Affected	Total Number Individuals Affected	Proportion Carriers
01	Comorbid Cases Social Phobia- MDD	22	5	27	0.8148
02	Non- Comorbid Cases Social Phobia	22	24	46	0.4783
03	Totals	44	29	73	0.6027
	Columns	01	02	03	03

Odds Ratio = 4.80 (95%CI: 1.55; 14.84)

Table C5T09 displays the two by two table and analysis for the Odds Ratio for the comorbidity for Major Depressive Disorder in subjects with Social Phobia, in SERT (s) allele carriers vs. non-carriers for in subjects

Table C5T10.Odds Ratio Comorbidity for Major Depressive Disorder in SERT S Allele Carriers/ Non-Carriers for Subjects with Agoraphobia

Rows	Grouping	SERT Carrier (ss+sl) Individuals Affected	SERT Non-Carrier (ll) Individuals Affected	Total Number Individuals Affected	Proportion Carriers
01	Comorbid Cases Agoraphobia- MDD	10	4	14	0.7143
02	Non- Comorbid Cases Agoraphobia	8	15	23	0.3478
03	Totals	18	19	37	0.4865
	Columns	01	02	03	03

Odds Ratio = 4.69 (95%CI: 1.11; 19.83)

Table C5T10 displays the two by two table and analysis for the Odds Ratio for the comorbidity for Major Depressive Disorder in subjects with Agoraphobia, in SERT (s) allele carriers vs. non-carriers for in subjects

Table C5T11. Number of Lifetime Prevalence Diagnoses Whole Sample (N=847)

Rows	# of Lifetime Prevalence Diagnoses	Number of Individuals Affected	Percent	Cumulative Percent
01	0	355	41.91	41.91
02	1	255	30.11	72.02
03	2	143	16.88	88.90
04	3	61	7.20	96.10
05	4	22	2.60	98.70
06	5	10	1.18	99.88
07	6	1	0.12	100.00
08	Totals	847	100.00	
	Columns	01	02	03

Table C5T11 Displays the subject distribution (individuals affected in each diagnostic group) for the number of lifetime prevalence diagnoses for the whole sample (N=847).

Table C5T12. Number of Lifetime Prevalence Diagnoses Stratified by Gender (N=816)

Rows	# of Lifetime Prevalence Diagnoses	Male Individuals Affected	Female Individuals Affected	Total Number Individuals Affected
01	0	106	218	324
02	1	113	142	255
03	2	49	94	143
04	3	15	46	61
05	4	7	15	22
06	5	4	6	10
07	6	0	1	1
08	Totals	294	522	816
	Columns	01	02	03

Significance Tests Number of Lifetime Prevalence Diagnoses by Gender (N=816)

Test	P Value
Pearson chi2(6)	0.035
Fisher's exact	0.027

Table C5T12 Displays the subject distribution and significance testing for the number of lifetime prevalence diagnoses stratified by gender (N=816).

Table C5T13. Number of Lifetime Prevalence Diagnoses Stratified by Median Age (44 y/o) (N=847)

Rows	# of Lifetime Prevalence Diagnoses	Age 44 & Younger Individuals Affected	Older Than 44 Individuals Affected	Total Number Individuals Affected
01	0	146	209	355
02	1	130	125	255
03	2	80	63	143
04	3	42	19	61
05	4	14	8	22
06	5	7	3	10
07	6	0	1	1
08	Totals	419	428	847
	Columns	01	02	03

Significance Tests Number of Lifetime Prevalence Diagnoses by Median Age (44 y/o) (N=847)

Test	P Value
Pearson chi2(6)	0.000
Fisher's exact	0.000

Table C5T13 Summarizes the subject distribution and significance testing for the number of lifetime prevalence diagnoses stratified by median age (44 y/o) (N=847).

Table C5T14. Number of Lifetime Prevalence Diagnoses Stratified by SERT (S) Carrier Status, Genotyped Sample (N=628)

Rows	# of Lifetime Prevalence Diagnoses	Non-Carriers SERT (LL) Individuals Affected	Carriers SERT(LS+ SS) Individuals Affected	Total Number Individuals Affected
01	0	120	147	267
02	1	82	100	182
03	2	46	60	106
04	3	21	27	48
05	4	5	9	14
06	5	5	5	10
07	6	1	0	1
08	Totals	280	348	628
	Columns	01	02	03

Significance Tests Number of Lifetime Prevalence Diagnoses by SERT (S) Carrier Status (N=628)

Test	P Value
Pearson chi2(6)	0.928
Fisher's exact	0.971

Table C5T14 Summarizes the subject distribution and significance testing for the number of lifetime prevalence diagnoses stratified by SERT (s) allele carrier status (N=628).

Table C5T15. Association of SERT Carrier Status with Prevalence of One or More LP Diagnosis (N=628)

Rows	Grouping	SERT Carrier (ss+sl) Individuals Affected	SERT Non-Carrier (ll) Individuals Affected	Total Number Individuals Affected
01	No Diagnosis LP	120	147	267
02	One or More Diagnosis LP	160	201	361
03	Totals	280	348	628
	Columns	01	02	03

Significance Tests SERT Carrier Status with Prevalence of One or More LP Diagnosis (N=628)

Test	OR (95% CI)	P Value
Odds Ratio Unadjusted	1.05 (0.76- 1.50)	0.75
Odds Ratio Adjusted	1.07 (0.75-1.55)	0.70

Table C5T15 displays the subject distribution into diagnostic categories stratified by SERT (s) allele carrier status (N=628).

Odds Ratio (95% CI) obtained from Logistic Regression models, display the risk for the carrier subgroup to be member of the category with the higher number of LP diagnoses. ORs were adjusted for gender, age, ethnicity, and marital status.

Table C5T16. Association of SERT Carrier Status with Prevalence of Two or More LP Diagnosis (N=628)

Rows	Grouping	SERT Carrier(ss+sl) Individuals Affected	SERT Non-Carrier (ll) Individuals Affected	Total Number Individuals Affected
01	One or Less Diagnosis LP	202	247	449
02	Two or More Diagnosis LP	78	101	179
03	Totals	280	348	628
	Columns	01	02	03

Significance Tests SERT Carrier Status with Prevalence of Two or More LP Diagnosis (N=628)

Test	OR (95% CI)	P Value
Odds Ratio Unadjusted	1.04 (0.63-1.69)	0.90
Odds Ratio Adjusted	1.12 (0.67-1.88)	0.66

Table C5T16 displays the subject distribution into diagnostic categories stratified by SERT (s) allele carrier status (N=628).

Odds Ratio (95% CI) obtained from Logistic Regression models, display the risk for the carrier subgroup to be member of the category with the higher number of LP diagnoses. ORs were adjusted for gender, age, ethnicity, and marital status.

TABLES FOR CHAPTER 06

Table C6T01A. Unweighted Lifetime Prevalence Psychiatric Disorders in Whole Sample per 100 Subjects (N=847)

Col	Psychiatric Disorder Lifetime Prevalence (LP)	# Subjects Affected	Lifetime Prevalence per 100 Subjects
01	Alcohol Dependence	177	20.90
02	Alcohol Abuse	48	5.67
03	Major Depressive Disorder	152	17.95
04	Bipolar Disorder	22	2.60
05	Psychotic Disorders	12	1.42
06	Panic Disorder	46	5.43
07	Agoraphobia	50	5.90
08	Social Phobia	100	11.81
09	Obsessive Compulsive Disorder	14	1.65
10	Generalized Anxiety Disorder	25	2.95
11	Anxiety Disorder NOS	21	2.48
12	Dysthymic Disorder	9	1.06
13	Depressive Disorder NOS	18	2.13
14	Simple Phobia Disorder	106	12.51
15	Adjust DO Depressed Mood	32	3.78
16	Opioid Dependence	36	4.25
17	Total Affected by LP Psychiatric Disorders	Total # Diagnoses Sample 868	Total Burden Mental Disorders Sample x100 Subj 102.48
	Row	01	02

Table C6T01A displays the unweighted lifetime prevalence estimates of the 16 selected mental disorders examined in our study sample. The column 01 displays the number of subjects in the sample diagnosed with each disorder, column 02 shows the unweighted lifetime prevalence estimates of each disorder per 100 subjects (Number of Individuals Diagnosed with a Disorder/ Total Number of Subjects in the Sample x 100). In row 17, column 01 displays the Total Number of Diagnoses in the sample (N=868). This number is the result of the simple addition of all the affected cases or diagnoses in our cohort. Row 17, column 02 displays the result of the quotient between the Total Number of Diagnoses in the sample, and the Total Number of Subjects in the sample (868 Diagnoses/ 847 Subjects= 1.028). This translates into a total lifetime prevalence burden of mental illness in the study sample of 102.48 cases of mental disorder per 100 subjects in the sample.

Table C6T01B Hypothetical Sample (N=10)

	No Diagnoses	One Diagnosis	Two Diagnoses	Three Diagnoses
I 01	X			
I 02	X			
I 03	X			
I 04		A		
I 05		A		
I 06		B		
I 07			A+B	
I 08			A+C	
I 09				A+C+D
I 10				B+C+D

Table C6T01B depicts a small hypothetical sample of 10 Individuals. Individuals 01, 02 and 03 received no diagnoses. Individuals 04 and 05 have been diagnosed only with Condition A. Individual 06 has been diagnosed only with Condition B. Individual 07 has been diagnosed with 2 conditions: Condition A, and B. Individual 08 has been diagnosed with 2 conditions: Condition A, and C. Individual 09 was diagnosed with 3 conditions: Conditions A, C, D.

Total Number of Individuals in the sample =10

Total number of Individuals Diagnosed = 7

Total Number of Diagnoses = 13.

Total Number of Comorbidities in the sample =16.

Comorbidity count by Individuals: Individuals 07 and 08 = 2 comorbidities each. Individuals 09 and 10 = 6 comorbidities each

Comorbidity count by diagnoses: Conditions A and D = 4 comorbidities each, Condition B= 3 comorbidities, Condition C = 5 comorbidities

Table C6T02A Comorbidity Matrix Table Axis I Psychiatric Disorders Lifetime Prevalence Whole Sample (N=847)

Row		Alcohol Dep	Alcohol Abuse	Major Depr DO	Bipolar Disorder	Psychotic Disorders	Panic Disorder	Agora phobia	Social Phobia	OCD	Gen Anx DO	Anxiety DO NOS	Dysthymic Disorder	Depressive DO NOS	Simple Phobia	Adjust DO Dep Mood	Opioid Dep	Total # Comorb
01	Alcohol Dependence	N/A	6	41	9	1	9	21	30	4	6	3	1	5	24	8	15	183
02	Alcohol Abuse	6	N/A	8	0	1	5	3	9	2	0	0	0	1	5	0	2	42
03	Major Depressive Disorder	41	8	N/A	0	3	18	18	32	7	10	6	3	2	26	1	11	186
04	Bipolar Disorder	9	0	0	N/A	0	4	4	6	2	0	0	0	0	1	0	0	26
05	Psychotic Disorders	1	1	3	0	N/A	0	2	2	0	0	1	0	1	3	0	0	14
06	Panic Disorder	9	5	18	4	0	N/A	9	11	2	2	0	0	1	7	2	4	74
07	Agoraphobia	21	3	18	4	2	9	N/A	19	4	4	3	1	1	13	1	3	106
08	Social Phobia	30	9	32	6	2	11	19	N/A	7	8	3	2	3	25	4	4	165
09	Obsessive Compulsive Disorder	4	2	7	2	0	2	4	7	N/A	2	0	1	0	4	0	0	35
10	Generalized Anxiety Disorder	6	0	10	0	0	2	4	8	2	N/A	0	2	0	9	1	0	44
11	Anxiety Disorder NOS	3	0	6	0	1	0	3	3	0	0	N/A	0	1	3	2	1	23
12	Dysthymic Disorder	1	0	3	0	0	0	1	2	1	2	0	N/A	0	2	0	0	12
13	Depressive Disorder NOS	5	1	2	0	1	1	1	3	0	0	1	0	N/A	2	0	4	21
14	Simple Phobia Disorder	24	5	26	1	3	7	13	25	4	9	3	2	2	N/A	10	4	138
15	Adjust DO Depressed Mood	8	0	1	0	0	2	1	4	0	1	2	0	0	10	N/A	0	29
16	Opioid Dependence	15	2	11	0	0	4	3	4	0	0	1	0	4	4	0	N/A	48
17	Total # Comorbidities	183	42	186	26	14	74	106	165	35	44	23	12	21	138	29	48	1146
18	# Axis I Diagnoses	177	48	152	22	12	46	50	100	14	25	21	9	18	106	32	36	868
19	Comorbidity/ Diagnosis Inflation Ratio	1.03	0.88	1.22	1.18	1.17	1.61	2.12	1.65	2.50	1.76	1.10	1.33	1.17	1.30	0.91	1.33	1.32
20	Standardized Comorbidity to Diagnosis Inflation Ratio	0.78	0.66	0.93	0.90	0.88	1.22	1.61	1.25	1.89	1.33	0.83	1.01	0.88	0.99	0.69	1.01	1.00
	Column	01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16	17

Table C6T02A. Rows 01 through 16 and Columns 01 through 16 display in each cell the tally of the number of comorbidity pairs or dyads. These represent the number of subjects in the sample that were diagnosed in their lifetime with the two conditions that are listed in the heading of the row and column that intersect in the selected cell. Row(r)01, column(c)08; as well as in r08, c01 displays 30 comorbidity pairs representing 30 subjects in the sample that were diagnosed both with Alcohol Dependence and Social Phobia in the sample. The cells of the row 17 from columns 01 through 16, as well as the cells of the column 17 form rows 01 through 16 display the total number of comorbidities for each individual disorder. The row 18, c01 through c16 displays the total number of subjects diagnosed for each individual Axis I mental disorder (identical to information presented in row 01 of Table 01). The cell in row 17 and column 17 displays the Total Number of Comorbidities in the sample (N=1146). The cell in the intersection of row 18 and column 17 displays the Total Number of Diagnoses in the sample (N=868). The cells in row 19, c01 through c16, represent the ratio of the number of Comorbidities to Number of Diagnoses in each disorder that we labeled with Comorbidity to Diagnosis Inflation Ratio (CDIR). The cell r19, c17, represents the CDIR of the whole sample. The row 20, c01 through c16, displays the standardized CDIR, of each disorder. These are the result of the CDIR of each disorder divided by the CDIR of the whole sample.

Table C6T02B. Unweighted Lifetime Prevalence Psychiatric Comorbidity Pairs per 100 Subjects (N=847)

Row		Alcohol Dep	Alcohol Abuse	Major Depr DO	Bipolar Disorder	Psychotic Disorders	Panic Disorder	Agora phobia	Social Phobia	OCD	Gen Anx DO	Anxiety DO NOS	Dysthymic Disorder	Depressive DO NOS	Simple Phobia	Adjust DO Dep Mood	Opioid Dep
01	Alcohol Dependence	N/A	0.71	4.84	1.06	0.12	1.06	2.48	3.54	0.47	0.71	0.35	0.12	0.59	2.83	0.95	1.77
02	Alcohol Abuse	0.71	N/A	0.95	0.00	0.12	0.59	0.35	1.06	0.24	0.00	0.00	0.00	0.12	0.59	0.00	0.24
03	Major Depressive Disorder	4.84	0.95	N/A	0.00	0.35	2.13	2.13	3.78	0.83	1.18	0.71	0.35	0.24	3.07	0.12	1.30
04	Bipolar Disorder	1.06	0.00	0.00	N/A	0.00	0.47	0.47	0.71	0.24	0.00	0.00	0.00	0.00	0.12	0.00	0.00
05	Psychotic Disorders	0.12	0.12	0.35	0.00	N/A	0.00	0.24	0.24	0.00	0.00	0.12	0.00	0.12	0.35	0.00	0.00
06	Panic Disorder	1.06	0.59	2.13	0.47	0.00	N/A	1.06	1.30	0.24	0.24	0.00	0.00	0.12	0.83	0.24	0.47
07	Agoraphobia	2.48	0.35	2.13	0.47	0.24	1.06	N/A	2.24	0.47	0.47	0.35	0.12	0.12	1.54	0.12	0.35
08	Social Phobia	3.54	1.06	3.78	0.71	0.24	1.30	2.24	N/A	0.83	0.95	0.35	0.24	0.35	2.95	0.47	0.47
09	Obsessive Comp Dis	0.47	0.24	0.83	0.24	0.00	0.24	0.47	0.83	N/A	0.24	0.00	0.12	0.00	0.47	0.00	0.00
10	Generalized Anx Dis	0.71	0.00	1.18	0.00	0.00	0.24	0.47	0.95	0.24	N/A	0.00	0.24	0.00	1.06	0.12	0.00
11	Anxiety Disorder NOS	0.35	0.00	0.71	0.00	0.12	0.00	0.35	0.35	0.00	0.00	N/A	0.00	0.12	0.35	0.24	0.12
12	Dysthymic Disorder	0.12	0.00	0.35	0.00	0.00	0.00	0.12	0.24	0.12	0.24	0.00	N/A	0.00	0.24	0.00	0.00
13	Depressive Dis NOS	0.59	0.12	0.24	0.00	0.12	0.12	0.12	0.35	0.00	0.00	0.12	0.00	N/A	0.24	0.00	0.47
14	Simple Phobia	2.83	0.59	3.07	0.12	0.35	0.83	1.54	2.95	0.47	1.06	0.35	0.24	0.24	N/A	1.18	0.47
15	Adjust DO Depr Mood	0.95	0.00	0.12	0.00	0.00	0.24	0.12	0.47	0.00	0.12	0.24	0.00	0.00	1.18	N/A	0.00
16	Opioid Dependence	1.77	0.24	1.30	0.00	0.00	0.47	0.35	0.47	0.00	0.00	0.12	0.00	0.47	0.47	0.00	N/A
	Column	01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16

Table C6T02B displays the prevalence of the comorbidity pairs per 100 individuals in the sample (N=847). The cells display the weight of each comorbidity pair (joint probability) for the sample as a whole. The comorbidity pair with the highest prevalence (0.0484 or 4.84%) was the one formed by those diagnosed with Major Depressive Disorder and Alcohol Dependence (r01, c03 and r03 c01). The second highest pair was the one comprised by those diagnosed with Major Depressive Disorder and Social Phobia (r03, c08 and r08, c03) presenting with a prevalence in the sample of 0.0378 or 3.78%.

Table C6T02C Comorbidity Pairs Prevalence as Percentage to Row Total Number of Diagnoses

Row		Alcohol Dep	Alcohol Abuse	Major Depr DO	Bipolar Disorder	Psychotic Disorders	Panic Disorder	Agora phobia	Social Phobia	OCD	Gen Anx DO	Anxiety DO NOS	Dysthymic Disorder	Depressive DO NOS	Simple Phobia	Adjust DO Dep Mood	Opioid Dep
01	Alcohol Dependence	N/A	3.39	23.16	5.08	0.56	5.08	11.86	16.95	2.26	3.39	1.69	0.56	2.82	13.56	4.52	8.47
02	Alcohol Abuse	12.50	N/A	16.67	0.00	2.08	10.42	6.25	18.75	4.17	0.00	0.00	0.00	2.08	10.42	0.00	4.17
03	Major Depressive Disorder	26.97	5.26	N/A	0.00	1.97	11.84	11.84	21.05	4.61	6.58	3.95	1.97	1.32	17.11	0.66	7.24
04	Bipolar Disorder	40.91	0.00	0.00	N/A	0.00	18.18	18.18	27.27	9.09	0.00	0.00	0.00	0.00	4.55	0.00	0.00
05	Psychotic Disorders	8.33	8.33	25.00	0.00	N/A	0.00	16.67	16.67	0.00	0.00	8.33	0.00	8.33	25.00	0.00	0.00
06	Panic Disorder	19.57	10.87	39.13	8.70	0.00	N/A	19.57	23.91	4.35	4.35	0.00	0.00	2.17	15.22	4.35	8.70
07	Agoraphobia	42.00	6.00	36.00	8.00	4.00	18.00	N/A	38.00	8.00	8.00	6.00	2.00	2.00	26.00	2.00	6.00
08	Social Phobia	30.00	9.00	32.00	6.00	2.00	11.00	19.00	N/A	7.00	8.00	3.00	2.00	3.00	25.00	4.00	4.00
09	Obsessive Comp Dis	28.57	14.29	50.00	14.29	0.00	14.29	28.57	50.00	N/A	14.29	0.00	7.14	0.00	28.57	0.00	0.00
10	Generalized Anx Dis	24.00	0.00	40.00	0.00	0.00	8.00	16.00	32.00	8.00	N/A	0.00	8.00	0.00	36.00	4.00	0.00
11	Anxiety Disorder NOS	14.29	0.00	28.57	0.00	4.76	0.00	14.29	14.29	0.00	0.00	N/A	0.00	4.76	14.29	9.52	4.76
12	Dysthymic Disorder	11.11	0.00	33.33	0.00	0.00	0.00	11.11	22.22	11.11	22.22	0.00	N/A	0.00	22.22	0.00	0.00
13	Depressive Dis NOS	27.78	5.56	11.11	0.00	5.56	5.56	5.56	16.67	0.00	0.00	5.56	0.00	N/A	11.11	0.00	22.22
14	Simple Phobia	22.64	4.72	24.53	0.94	2.83	6.60	12.26	23.58	3.77	8.49	2.83	1.89	1.89	N/A	9.43	3.77
15	Adjust DO Depr Mood	25.00	0.00	3.13	0.00	0.00	6.25	3.13	12.50	0.00	3.13	6.25	0.00	0.00	31.25	N/A	0.00
16	Opioid Dependence	41.67	5.56	30.56	0.00	0.00	11.11	8.33	11.11	0.00	0.00	2.78	0.00	11.11	11.11	0.00	N/A
	Column	01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16

Table C6T02C Comorbidity and Diagnosis Composition as Row Percentage. Rows 01 through 16 display the comorbidity composition (as percentages) of the Axis I disorders that appear in the heading of each row. Row 03 displays how the rest of the Axis I disorders impact on the comorbidity makeup of Major Depressive Disorder. In probability terms, the value in each cell represents the conditional probability of the condition that appears in the heading of the column given the condition that appears in the heading of the row. As an example, the condition probability of Social Phobia, given the subject has Major Depressive Disorder is 32/152= 0.2105 or 21.05% (r03, c08). On the other hand, the conditional probability that a subject has Major Depressive Disorder given he/she has Social Phobia is 32/100= 0.32 or 32% (r08, c03).

Table C6T02D Comorbidity Pairs as Ratio of Conditional to Marginal Probability (RCMP)

Row		Alcohol Dep	Alcohol Abuse	Major Depr DO	Bipolar Disorder	Psychotic Disorders	Panic Disorder	Agora phobia	Social Phobia	OCD	Gen Anx DO	Anxiety DO NOS	Dysthymic Disorder	Depressive DO NOS	Simple Phobia	Adjust DO Dep Mood	Opioid Dep
01	Alcohol Dependence	N/A	0.60	1.29	1.96	0.40	0.94	2.01	1.44	1.37	1.15	0.68	0.53	1.33	1.08	1.20	1.99
02	Alcohol Abuse	0.60	N/A	0.93	0.00	1.47	1.92	1.06	1.59	2.52	0.00	0.00	0.00	0.98	0.83	0.00	0.98
03	Major Depressive Disorder	1.29	0.93	N/A	0.00	1.39	2.18	2.01	1.78	2.79	2.23	1.59	1.86	0.62	1.37	0.17	1.70
04	Bipolar Disorder	1.96	0.00	0.00	N/A	0.00	3.35	3.08	2.31	5.50	0.00	0.00	0.00	0.00	0.36	0.00	0.00
05	Psychotic Disorders	0.40	1.47	1.39	0.00	N/A	0.00	2.82	1.41	0.00	0.00	3.36	0.00	3.92	2.00	0.00	0.00
06	Panic Disorder	0.94	1.92	2.18	3.35	0.00	N/A	3.31	2.03	2.63	1.47	0.00	0.00	1.02	1.22	1.15	2.05
07	Agoraphobia	2.01	1.06	2.01	3.08	2.82	3.31	N/A	3.22	4.84	2.71	2.42	1.88	0.94	2.08	0.53	1.41
08	Social Phobia	1.44	1.59	1.78	2.31	1.41	2.03	3.22	N/A	4.23	2.71	1.21	1.88	1.41	2.00	1.06	0.94
09	Obsessive Comp Dis	1.37	2.52	2.79	5.50	0.00	2.63	4.84	4.24	N/A	4.84	0.00	6.72	0.00	2.28	0.00	0.00
10	Generalized Anx Dis	1.15	0.00	2.23	0.00	0.00	1.47	2.71	2.71	4.84	N/A	0.00	7.53	0.00	2.88	1.06	0.00
11	Anxiety Disorder NOS	0.68	0.00	1.59	0.00	3.36	0.00	2.42	1.21	0.00	0.00	N/A	0.00	2.24	1.14	2.52	1.12
12	Dysthymic Disorder	0.53	0.00	1.86	0.00	0.00	0.00	1.88	1.88	6.72	7.53	0.00	N/A	0.00	1.78	0.00	0.00
13	Depressive Dis NOS	1.33	0.98	0.62	0.00	3.92	1.02	0.94	1.41	0.00	0.00	2.24	0.00	N/A	0.89	0.00	5.23
14	Simple Phobia	1.08	0.83	1.37	0.36	2.00	1.22	2.08	2.00	2.28	2.88	1.14	1.78	0.89	N/A	2.50	0.89
15	Adjust DO Depr Mood	1.20	0.00	0.17	0.00	0.00	1.15	0.53	1.06	0.00	1.06	2.52	0.00	0.00	2.50	N/A	0.00
16	Opioid Dependence	1.99	0.98	1.70	0.00	0.00	2.05	1.41	0.94	0.00	0.00	1.12	0.00	5.23	0.89	0.00	N/A
	Column	01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16

Table C6T02D displays the values of the Ratio of Conditional to Marginal Probabilities (RCMP) for all comorbidity dyads in the sample. If we define that a comorbidity dyad is integrated by Condition A and Condition B. The values displayed in the cells con be defined as PA/B / PA, the conditional probability of the Condition A given the Condition B divided by the probability of the Condition A. In probability terms, the ratio of PA/B /PA is identical to PB/A / PB, the conditional probability of Condition B given A divided by the Probability of Condition B. In r01, c03 and r03, c01 we can read the value of 1.29. This can be described as the probability of a diagnoses of Major Depressive Disorder in subjects diagnosed with Alcohol Dependence divided by the probability of a diagnoses of Major Depressive Disorder in the whole sample. It can also be described as the probability of a diagnoses of Alcohol Dependence in individuals already diagnosed with Major Depressive Disorder divided by the probability of Alcohol Dependence in the whole sample.

*Table C6T02E Comorbidity Odds Ratio (N=847) * Represents ORs significant <.05*

Row		Alcohol Dep	Alcohol Abuse	Major Depr DO	Bipolar Disorder	Psychotic Disorders	Panic Disorder	Agora phobia	Social Phobia	OCD	Gen Anx DO	Anxiety DO NOS	Dysthymic Disorder	Depressive DO NOS	Simple Phobia	Adjust DO Dep Mood	Opioid Dep
01	Alcohol Dependence	N/A	0.52	1.52*	2.71*	0.34	0.92	2.98*	1.75*	1.53	1.20	0.62	0.47	1.47	1.12	1.27	2.86*
02	Alcohol Abuse	0.52	N/A	0.91		1.52	2.15	1.07	1.80	2.85				0.98	0.80		0.98
03	Major Depressive Disorder	1.52*	0.91	N/A		1.53	3.20*	2.78*	2.46*	4.74*	3.19*	1.86	2.31	0.57	1.59	0.14	2.09*
04	Bipolar Disorder	2.71*			N/A		4.14*	3.76*	2.92*	6.78*					0.33		
05	Psychotic Disorders	0.34	1.52	1.53		N/A		3.28	1.50			3.70		4.37	2.37		
06	Panic Disorder	0.92	2.15	3.20*	4.14*		N/A	4.51*	2.51*	2.99	1.54			1.02	1.27	1.17	2.29
07	Agoraphobia	2.98*	1.07	2.78*	3.76*	3.28	4.51*	N/A	5.42*	6.84*	3.21*	2.76	2.01	0.94	2.66*	0.50	1.48
08	Social Phobia	1.75*	1.80	2.46*	2.92*	1.50	2.51*	5.42*	N/A	7.96*	3.73*	1.25	2.16	1.51	2.74*	1.07	0.93
09	Obsessive Compulsive Disorder	1.53	2.85	4.74*	6.78*		2.99	6.84*	7.96*	N/A	5.87*		7.93		2.87		
10	Generalized Anxiety Disorder	1.20		3.19*			1.54	3.21*	3.73*	5.87*	N/A		10.12*		4.20*	1.06	
11	Anxiety Disorder NOS	0.62		1.86		3.70		2.76	1.25			N/A		2.38	1.17	2.79	1.13
12	Dysthymic Disorder	0.47		2.31				2.01	2.16	7.93	10.12*		N/A	A	2.02		
13	Depressive Disorder NOS	1.47	0.98	0.57		4.37	1.02	0.94	1.51			2.38		N/A	0.87		7.12*
14	Simple Phobia Disorder	1.12	0.80	1.59	0.33	2.37	1.27	2.66*	2.74*	2.87	4.20*	1.17	2.02	0.87	N/A	3.40*	0.87
15	Adjust DO Depressed Mood	1.27		0.14			1.17	0.50	1.07		1.06	2.79			3.40*	N/A	
16	Opioid Dependence	2.86*	0.98	2.09*			2.29	1.48	0.93			1.13		7.12*	0.87		N/A
	Column	01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16

Table C6T02E displays the Odds Ratio (OR) of the lifetime prevalence comorbidity pairs for all 16 Axis I disorders. We can see that the RCMP values have the same direction that the ORs, being somewhat more conservative. The ORs have the added advantage of a significance testing, although they are far more time demanding in their execution than the RCMP.

Table C6T03A Lifetime Prevalence Axis I Disorders (unweighted). Divided by Diagnostic Groups. (N=847)

Row		No Diag DG0	One Diag DG1	Two Diag DG2	Three Diag DG3	Four Diag DG4	Five Diag DG5	Six Diag DG6	Totals
01	Alcohol Dependence	0	69	60	28	14	5	1	177
02	Alcohol Abuse	0	24	12	8	2	2	0	48
03	Major Depressive Disorder	0	50	48	33	13	7	1	152
04	Bipolar Disorder	0	8	7	3	3	1	0	22
05	Psychotic Disorders	0	2	6	4	0	0	0	12
06	Panic Disorder	0	8	15	13	7	3	0	46
07	Agoraphobia	0	6	11	13	12	7	1	50
08	Social Phobia	0	15	40	22	12	10	1	100
09	Obsessive Compulsive DO	0	1	3	2	4	4	0	14
10	Generalized Anxiety Disorder	0	7	2	8	6	2	0	25
11	Anxiety Disorder NOS	0	6	10	4	0	0	1	21
12	Dysthymic Disorder	0	3	3	1	1	1	0	9
13	Depressive Disorder NOS	0	7	6	2	2	0	1	18
14	Simple Phobia Disorder	0	28	39	26	5	8	0	106
15	Adjust DO Depressed Mood	0	10	16	5	1	0	0	32
16	Opioid Dependence	0	11	8	11	6	0	0	36
17	#Diagnoses Per Group DG	0	255	286	183	88	50	6	868
18	# Individuals Diagnosed	0	255	143	61	22	10	1	492
19	# Individuals	355	255	143	61	22	10	1	847
	Column	01	02	03	04	05	06	07	08

Table C6T03A details the data of the grouping or stratification of the 847 individuals in the sample. Column 01 displays the individuals that did not receive any Axis I diagnosis. Columns 02 through 07, rows 01 through 16 display the number of subjects diagnosed with a mental disorder in each diagnostic group. The cells of column 08 display the total number of diagnoses for the individual Axis I disorders. Row 17 contains the number of diagnoses accrued by each diagnostic group (DG0=0, DG1=255, DG2=286, DG3=183, DG4=88, DG5=50, and DG6=6) and by the total sample (N=868). Row 18 displays the number of individuals that received a diagnosis in each group (DG0=0, DG1=255, DG2=143, DG3=61, DG4=22, DG5=10, and DG6=1) as well as in the total sample (N=492). Row 19 displays the number of individuals in each group (in columns 01 through 07) and in the total sample (in column 08).

Table C6T03B Lifetime Prevalence Selected Disorders (unweighted). Divided by Diagnostic Groups. Row Percentage (N=847)

Row		No Diag DG0	One Diag DG1	Two Diag DG2	Three Diag DG3	Four Diag DG4	Five Diag DG5	Six Diag DG6	Total %
01	Alcohol Dependence	0.00	38.98	33.90	15.82	7.91	2.82	0.56	100
02	Alcohol Abuse	0.00	50.00	25.00	16.67	4.17	4.17	0.00	100
03	Major Depressive Disorder	0.00	32.89	31.58	21.71	8.55	4.61	0.66	100
04	Bipolar Disorder	0.00	36.36	31.82	13.64	13.64	4.55	0.00	100
05	Psychotic Disorders	0.00	16.67	50.00	33.33	0.00	0.00	0.00	100
06	Panic Disorder	0.00	17.39	32.61	28.26	15.22	6.52	0.00	100
07	Agoraphobia	0.00	12.00	22.00	26.00	24.00	14.00	2.00	100
08	Social Phobia	0.00	15.00	40.00	22.00	12.00	10.00	1.00	100
09	Obsessive Compulsive DO	0.00	7.14	21.43	14.29	28.57	28.57	0.00	100
10	Generalized Anxiety Disorder	0.00	28.00	8.00	32.00	24.00	8.00	0.00	100
11	Anxiety Disorder NOS	0.00	28.57	47.62	19.05	0.00	0.00	4.76	100
12	Dysthymic Disorder	0.00	33.33	33.33	11.11	11.11	11.11	0.00	100
13	Depressive Disorder NOS	0.00	38.89	33.33	11.11	11.11	0.00	5.56	100
14	Simple Phobia Disorder	0.00	26.42	36.79	24.53	4.72	7.55	0.00	100
15	Adjust DO Depressed Mood	0.00	31.25	50.00	15.63	3.13	0.00	0.00	100
16	Opioid Dependence	0.00	30.56	22.22	30.56	16.67	0.00	0.00	100
17	#Diagnoses Per Group DG (as percentages of N=868)	0.00	29.38	32.95	21.08	10.14	5.76	0.69	100
18	# Individuals Diagnosed (as percentages of N=492)	0.00	51.83	29.07	12.40	4.47	2.03	0.20	100
19	# Individuals (as percentages of N=847)	41.91	30.11	16.88	7.20	2.60	1.18	0.12	100
	Column	01	02	03	04	05	06	07	08

Table C6T03B displays the information of table 03A as percentages of the total row counts contained in Column 08. Column 01 displays the individuals that did not receive any Axis I diagnosis. Columns 02 through 07, rows 01 through 16 display the percentage of subjects diagnosed in each diagnostic group with all the individual Axis I disorders. Row 17 contains the number of diagnoses accrued by each diagnostic group as percentages of the total number of diagnoses in the sample (n=868) (DG0=0%, DG1=29.38%, DG2=32.95%, DG3=21.08%, DG4=10.14%, DG5=5.76%, DG6=0.69%). Row 18 displays the number of individuals that received a diagnosis in each group as percentages of the total number of individuals diagnosed (N=492) (DG0=0%, DG1=51.83%, DG2=29.07%, DG3=12.40%, DG4=4.47%, DG5=2.03%, DG6=0.20%). Row 19 displays the number of individuals in each group as percentages of the total number of Individuals in the Sample (N=847).

Table C6T03C. Adjustment Process. The Diagnostic and Comorbidity Inflation Ratios

Row		Unadjusted # Diagnoses	Adjusted # Diagnoses	Diagnostic Proportion After Adjustment	Diagnostic Inflation Ratio (DIR) (Unadj/ Adj)	Standardized DIR Adjusted (to Total DIR Sample)	# Comorbidities	Comorb Inflation Ratio (CIR) Comorb/ Adj Diag	StandardCIR (Adjusted To CIR Total Sample)	Unadj Lifetime Preval X 100 Subjects	Adjusted Lifetime Preval X100 Subjects
01	Alcohol Dependence	177	113.00	0.64	1.57	0.89	183	1.62	0.70	20.90	13.34
02	Alcohol Abuse	48	33.57	0.70	1.43	0.81	42	1.25	0.54	5.67	3.96
03	Major Depressive Disorder	152	89.82	0.59	1.69	0.96	186	2.07	0.89	17.95	10.60
04	Bipolar Disorder	22	13.45	0.61	1.64	0.93	26	1.93	0.83	2.60	1.59
05	Psychotic Disorders	12	6.33	0.53	1.89	1.07	14	2.21	0.95	1.42	0.75
06	Panic Disorder	46	22.18	0.48	2.07	1.18	74	3.34	1.43	5.43	2.62
07	Agoraphobia	50	20.40	0.41	2.45	1.39	106	5.20	2.23	5.90	2.41
08	Social Phobia	100	47.50	0.48	2.11	1.19	165	3.47	1.49	11.81	5.61
09	Obsessive Comp DO	14	4.97	0.35	2.82	1.60	35	7.05	3.02	1.65	0.59
10	Generalized Anxiety DO	25	12.57	0.50	1.99	1.13	44	3.50	1.50	2.95	1.48
11	Anxiety Disorder NOS	21	12.50	0.60	1.68	0.95	23	1.84	0.79	2.48	1.48
12	Dysthymic Disorder	9	5.28	0.59	1.70	0.97	12	2.27	0.97	1.06	0.62
13	Depressive Disorder NOS	18	11.33	0.63	1.59	0.90	21	1.85	0.80	2.13	1.34
14	Simple Phobia Disorder	106	59.02	0.56	1.80	1.02	138	2.34	1.00	12.51	6.97
15	Adjust DO Depressed Mood	32	19.92	0.62	1.61	0.91	29	1.46	0.63	3.78	2.35
16	Opioid Dependence	36	20.17	0.56	1.79	1.01	48	2.38	1.02	4.25	2.38
17	Totals	Tot # Diagnoses: 868	Total #Adj Diag: 492	Diagnostic Proportion After Adjustment 0.57	DIR Whole Sample: 1.76	SDIR: 1	Total # Comorbidities: 1146	CIR Whole Sample 2.33	SCIR: 1	Unadjust Burden: 102.48	Adjusted Burden: 58.09
	Column	01	02	03	04	05	06	07	08	09	10

Table C6T03C displays the result of the adjustment and ratios. Column 01, row 01 through row 16 displays the number of unadjusted diagnoses for each disorder. Column 01, row 17, the total number of diagnoses in the sample (N=868). Column 02, rows 01 through 16, displays the number of adjusted diagnoses. Column 02, row 17, the total number of adjusted diagnoses in the sample (N=492). Column 03, rows 01 through 16, displays proportion of diagnostic information after adjustment for each disorder. Column 03, row 17, displays proportion of total diagnostic proportion after adjustment. This is a measure of the extent of the adjustment. Column 04, rows 01 through 16, displays the Diagnostic Inflation Ratio (DIR) (Unadjusted # Diagnoses/ Adjusted # Diagnoses) for each disorder. Column 04, row 17, displays the DIR for the whole sample. Column 05, rows 01 through 16, displays the Standardized Diagnostic Inflation Ratio (SDIR) for each disorder (DIR of each disorder/ DIR whole sample). Column 06, row 01 through row 16 displays the number of comorbidities for each disorder. Column 07, row 17, the total number of comorbidities in the sample (N=1146). Column 07, rows 01 through 16, displays the Comorbidity Inflation Ratio (CIR) (Unadjusted # Comorbidities/ Adjusted # Diagnoses) for each disorder. Column 07, row 17, displays the CIR for the whole sample. Column 08, rows 01 through 16, displays the Standardized Comorbidity Inflation Ratio (SCIR) for each disorder (CIR of each disorder/ CIR whole sample). Column 09, rows 01 through 16, displays the Unadjusted Lifetime Prevalence Estimates per 100 subjects for the Whole Sample. Column 09, row 17, displays the unadjusted burden of mental disorders per 100 subjects for the whole sample (102.48). Column 10, rows 01 through 16, displays the Adjusted Lifetime Prevalence Estimates per 100 subjects for the Whole Sample (Adjusted Number of Diagnoses/ Sample Size). Column 10, row 17, displays the adjusted burden of mental disorders per 100 subjects for the whole sample (58.09).

Column 01

Unadjusted Number of Diagnoses for Individual Disorders (rows 01-16), and for total number of disorders per diagnostic group (row17) =

= # Diagnoses in DG1 + # Diagnoses in DG2 + # Diagnoses in DG3 + # Diagnoses in DG4 + # Diagnoses in DG5 + # Diagnoses in DG6

Column 02

Adjusted Number of Diagnoses for Individual Disorders (rows 01-16), and for total number of disorders per diagnostic group (row17) =

= # Diagnoses in DG1 /1 + # Diagnoses in DG2 /2 + # Diagnoses in DG3 /3 + # Diagnoses in DG4 /4 + # Diagnoses in DG5 / 5 + # Diagnoses in DG6 /6

Column 03

Diagnostic Proportion Post Adjustment for Individual Disorders= Adjusted Number of Diagnoses Disorder A / Unadjusted Number of Diagnoses Disorder A

Diagnostic Proportion Post Adjustment for Total # Disorders= Adjusted Total Number of Diagnoses / Unadjusted Total Number of Diagnoses

Column 04

Diagnostic Inflation Ratio (DIR) for Individual Disorders= Unadjusted Number of Diagnoses Disorder A / Adjusted Number of Diagnoses Disorder A

Diagnostic Inflation Ratio (DIR) for Total # Disorders = Unadjusted Total Number of Diagnoses / Adjusted Total Number of Diagnoses

Column 05

Standardized Diagnostic Inflation Ratio = DIR of Individual Disorder / DIR Total # Disorders

Column 06

Unadjusted number of Comorbidites = Can be Obtained from Row 17, Table C6T02A or can be calculated as

= # Diagnoses in DG1 x 0 + # Diagnoses in DG2 x 2 + # Diagnoses in DG3 x 6 + # Diagnoses in DG4 x 12 + # Diagnoses in DG5 x 20 + # Diagnoses in DG6 x 30

Column 07

Comorbidity Inflation Ratio (CIR) for Individual Disorders= Number of Comorbidities Disorder A / Adjusted Number of Diagnoses Disorder A

Comorbidity Inflation Ratio (CIR) for Total # Disorders= Total Number of Comorbidities / Adjusted Total Number of Diagnoses

Column 08

Standardized Comorbidity Inflation Ratio = CIR of Individual Disorder /CIR Total # Disorders

Column 09

Unadjusted Lifetime Prevalence x 100 Subjects for Individual Disorders = Unadjusted Number of Diagnoses Disorder A x 100 / Sample Size (847)

Unadjusted Burden for Total # Mental Disorders in Whole Sample x 100 Subjects = Unadjusted Total Number of Diagnoses x 100/ Sample Size (847)

Column 10

Adjusted Lifetime Prevalence x 100 Subjects for Individual Disorders = Adjusted Number of Diagnoses Disorder A x 100 / Sample Size (847)

Adjusted Burden for Total # Mental Disorders in Whole Sample x 100 Subjects = Adjusted Total Number of Diagnoses x 100/ Sample Size (847)

Table C6T03D. Example on the Table for Chi Square and Fisher's Exact Test Calculation

	DG1	*DG2*	*DG3*	*DG4*	*DG5*	*DG6*	*Totals*
# Diagnoses Alcohol Dependence	*69*	*60*	*28*	*14*	*5*	*1*	*177*
# Rest of Diagnoses	*186*	*226*	*155*	*74*	*45*	*5*	*691*
Total of Diagnoses In each DG	*255*	*286*	*183*	*88*	*50*	*6*	*868*

Table C6T03D Display the diagnostic distribution of the individuals diagnosed with Alcohol Dependence across the diagnostic strata

Table C6T03E. Results for the Chi Square and Fisher's Exact Test Significance Test on all 16 Axis I Conditions

	Inference on Total Number of Diagnoses		
Row	*Axis I Condition*	*Chi2 p values*	*Exact Test p values*
01	*Alcohol Dependence*	*0.013**	*0.013**
02	*Alcohol Abuse*	*0.048**	*0.082*
03	*Major Depressive Disorder*	*0.876*	*0.887*
04	*Bipolar Disorder*	*0.917*	*0.875*
05	*Psychotic Disorders*	*0.463*	*0.496*
06	*Panic Disorder*	*0.394*	*0.335*
07	*Agoraphobia*	*0.000**	*0.000**
08	*Social Phobia*	*0.017**	*0.007**
09	*Obsessive Compulsive DO*	*0.001**	*0.004**
10	*Generalized Anxiety Disorder*	*0.040**	*0.019**
11	*Anxiety Disorder NOS*	*0.074*	*0.123*
12	*Dysthymic Disorder*	*0.962*	*0.795*
13	*Depressive Disorder NOS*	*0.117*	*0.232*
14	*Simple Phobia Disorder*	*0.253*	*0.251*
15	*Adjust DO Depressed Mood*	*0.206*	*0.268*
16	*Opioid Dependence*	*0.226*	*0.217*
	Column	*01*	*02*

Table C6T03E displays the results of the Chi Square and Fisher Exact Tests done for each of the Axis I conditions. The p<0.05 are marked with an asterisk. The results show that Alcohol Dependence, Agoraphobia, Social Phobia, Obsessive Compulsive Disorder, and Generalized Anxiety Disorder have a distribution of individuals diagnosed across the Diagnostic Strata that differs significantly from the one of the total sample.

Table C6T04. Diagnoses and Comorbidities by Diagnostic Groups (N=847)

Row		No Diag DG0		One Diag DG1		Two Diag DG2		Three Diag DG3		Four Diag DG4		Five Diag DG5		Six Diag DG6		Totals	
		Diag	Com	Diag	Com	Diag	Com	Diag	Com	Diag	Com	Diag	Com	Diag	Com	Diag	Com
01	Alcohol Dependence	0	0	69	0	60	60	28	56	14	42	5	20	1	5	177	183
02	Alcohol Abuse	0	0	24	0	12	12	8	16	2	6	2	8	0	0	48	42
03	Major Depressive Disorder	0	0	50	0	48	48	33	66	13	39	7	28	1	5	152	186
04	Bipolar Disorder	0	0	8	0	7	7	3	6	3	9	1	4	0	0	22	26
05	Psychotic Disorders	0	0	2	0	6	6	4	8	0	0	0	0	0	0	12	14
06	Panic Disorder	0	0	8	0	15	15	13	26	7	21	3	12	0	0	46	74
07	Agoraphobia	0	0	6	0	11	11	13	26	12	36	7	28	1	5	50	106
08	Social Phobia	0	0	15	0	40	40	22	44	12	36	10	40	1	5	100	165
09	Obsessive Compulsive Disorder	0	0	1	0	3	3	2	4	4	12	4	16	0	0	14	35
10	Generalized Anxiety Disorder	0	0	7	0	2	2	8	16	6	18	2	8	0	0	25	44
11	Anxiety Disorder NOS	0	0	6	0	10	10	4	8	0	0	0	0	1	5	21	23
12	Dysthymic Disorder	0	0	3	0	3	3	1	2	1	3	1	4	0	0	9	12
13	Depressive Disorder NOS	0	0	7	0	6	6	2	4	2	6	0	0	1	5	18	21
14	Simple Phobia Disorder	0	0	28	0	39	39	26	52	5	15	8	32	0	0	106	138
15	Adjust DO Depressed Mood	0	0	10	0	16	16	5	10	1	3	0	0	0	0	32	29
16	Opioid Dependence	0	0	11	0	8	8	11	22	6	18	0	0	0	0	36	48
17	#Diagnoses	0		255		286		183		88		50		6		868	
18	# Comorbidities		0		0		286		366		264		200		30		1146
19	#Individuals Diagnosed	0		255		143		61		22		10		1		492	
20	#Individuals	355		255		143		61		22		10		1		847	
	Columns	01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16

Table C6T04 details the data of the grouping or stratification of the 847 individuals in the sample. Columns 01 through 14, rows 01 through 16 display the number of diagnoses and comorbidities in each diagnostic group. Column 15, rows 01 through 16 display the total diagnoses for the individual Axis I disorders. Column 16, rows 01 through 16 display the total comorbidities for the individual Axis I disorders. Row 17 contains the number of diagnoses accrued by each diagnostic group (DG0=0, DG1=255, DG2=286, DG3=183, DG4=88, DG5=50, and DG6=6) and by the total sample (N=868). Row 18 contains the number of comorbidities accrued by each diagnostic group (DG0=0, DG1=0, DG2=286, DG3=366, DG4=264, DG5=200, and DG6=30) and by the total sample (N=1146). Row 19 displays the number of individuals that received a diagnosis in each group (DG0=0, DG1=255, DG2=143, DG3=61, DG4=22, DG5=10, and DG6=1) as well as in the total sample (N=492). Row 20 displays the number of individuals in each group (in columns 01 through 07) and in the total sample (in column 08).

Table C6T05 List of Developed Measures, Description, Potential Uses

Instrument	*Description*	*Use*
Diagnostic Proportion Post Adjustment	*Ratio = Adjusted Number of Diagnoses / Unadjusted Number of Diagnoses* *Both for the Total Number of Diagnoses as well as the Individual Disorders* *It is a measure of the diagnostic information remaining after the adjustment process. The higher the comorbidity burden of a total sample or an individual diagnosis, the lower the proportion will remain.*	*Provides a measure of the significance of the comorbidity burden for the individual disorders and for the whole sample (using proportion testing)*
Diagnostic Inflation Ratio (DIR)	*Ratio = Unadjusted Number of Diagnoses / Adjusted Number of Diagnoses* *Both for the Total Number of Diagnoses as well as for the Individual Disorders*	*It is the expected or mean number of diagnoses for any diagnosed participant selected at random. The DIR of the whole sample can characterize the sample's diagnostic burden.*
Standardized Diagnostic Inflation Ratio (SDIR)	*Ratio = Diagnostic Inflation Ratio for Individual Disorder / Diagnostic Inflation Ratio for the Whole Sample* *For Individual Disorders*	*It is a measure of the difference in the expected diagnosis for each disorder, compared to the DIR for the whole sample*
Comorbidity Inflation Ratio (CIR)	*Ratio = Unadjusted Number of Comorbidities / Adjusted Number of Diagnoses* *Both for the Total Number of Comorbidities as well as the Individual Disorders*	*It is the expected or mean number of comorbidities for any diagnosed participant selected at random. The CIR of the whole sample can characterize the sample's comorbidity burden.*
Standardized Comorbidity Inflation Ratio (SCIR)	*Ratio = Comorbidity Inflation Ratio for Individual Disorder / Comorbidity Inflation Ratio for the Whole Sample* *For Individual Disorders*	*It is a measure of the difference in expected comorbidities for each disorder, compared to the CIR for the whole sample*
Comorbidity to Diagnoses Inflation Ratio (CDIR)	*Ratio = Unadjusted Number of Comorbidities / Unadjusted Number of Diagnoses* *Can also be calculated by = CIR / DIR* *Both for the Total Number of Comorbidities as well as the Individual Disorders*	*The CDIR is the ratio of comorbidities to diagnoses for each condition and for the whole sample*
Standardized Comorbidity to Diagnoses Inflation Ratio (SCDIR)	*Ratio = CDIR for Individual Disorder / CIDR for the Whole Sample* *For Individual Disorders*	*It is a measure of the difference in expected ratio of comorbidity to diagnosis for each disorder, compared to the CDIR for the whole sample*

Table C6T05 Lists the Proposed Measures, with a brief description

CHAPTER 07: TABLES

Table C7T01. Number of Events (Lifetime Prevalence Diagnoses), Number of Person-Years, and Incidence Rate x 1000 patients for Whole Sample (N=847), SERT (s) Allele Carriers (N=336) and Non-Carriers (N=266)

		Whole Sample N=847			SERT (S) Allele Carrier (LS+ SS) N=336			SERT (S) Allele Non-Carrier (LL)N=226		
Row		# LP Diag	Total Person-Years	Incidence Rate	# LP Diag	Total Person-Years	Incidence Rate	# LP Diag	Total Person-Years	Incidence Rate
01	Alcohol Dep	200	36408	5.49	85	14931	5.69	60	11422	5.25
02	Major Depr DO	143	37836	3.78	61	15310	3.98	50	11858	4.22
03	Bipolar DO	14	39185	0.36	5	15883	0.31	4	12352	0.33
04	Psychotic Dos	10	39187	0.26	2	15934	0.13	2	12384	0.16
05	Panic Disorder	42	38998	1.08	24	15727	1.52	7	12377	0.57
06	Agoraphobia	46	38466	1.20	17	15596	1.09	17	12092	1.41
07	Social Phobia	93	36685	2.54	41	14740	2.78	25	11718	2.13
08	Obs Comp DO	12	39175	0.31	1	15954	0.06	6	12285	0.49
09	Gen Anx DO	22	39068	0.56	8	15851	0.50	8	12267	0.65
10	Simple Phobia	92	36106	2.55	37	14612	2.53	39	11094	3.52
11	Opioid Dep	10	38291	0.26	3	15566	0.19	4	12095	0.33
	Column	01	02	03	04	05	06	07	08	09

Table C7P1T01 summarizes the number of events (Lifetime Prevalence Diagnoses), the Total Person-Years for each disorder, and, the corresponding Incidence Rate per 1000 person-years, for the Whole Sample (N=847), SERT (s) Allele Carrier (N=336), and Non-Carriers (N=266)

Table C7T02. Time to Event Estimates SERT S Allele Carriers vs Non Carriers (Non-Carriers N=266/ Carriers N=336)

		Incidence Rate Ratio (IRR) (95% CI)	IRR p-value	Log Rank P value	Unadjusted Hazard Ratio (95%CI)	Unadjusted Hazard Ratio p-value	Adjusted Hazard Ratio (95%CI)	Adjusted Hazard Ratio p-value
01	Alcohol Dependence	1.08 (0.77-1.53)	0.64	0.72	1.06 (0.76-1.48)	0.72	1.05 (0.75-1.48)	0.78
02	Major Depr DO	0.94 (0.64-1.40)	0.76	0.76	0.94 (0.65-1.37)	0.76	0.93 (0.63-1.36)	0.69
03	Bipolar DO	0.97 (0.21-4.90)	0.96	0.98	0.99 (0.26-3.67)	0.98	0.82 (0.22-3.09)	0.76
04	Psychotic Dos	0.78 (0.06-10.72)	0.81	0.82	0.79 (0.11-5.63)	0.82	0.85 (0.11-6.46)	0.88
05	Panic Disorder	2.70 (1.13-7.42)	0.01	0.02	2.63 (1.13-6.10)	0.03	2.35 (1.00-5.51)	0.05
06	Agoraphobia	0.78 (0.37-1.62)	0.46	0.45	0.77 (0.39-1.51)	0.45	0.77 (0.39-1.53)	0.46
07	Social Phobia	1.30 (0.77-2.24)	0.30	0.21	1.37 (0.83-2.25)	0.22	1.35 (0.81-2.27)	0.25
08	Obs Comp DO	0.13 (0.00-0.99)	0.03	0.03	0.13 (0.16-1.09)	0.06	0.11 (0.01-0.95)	0.04
09	Gen Anxiety DO	0.77 (0.25-2.37)	0.61	0.63	0.78 (0.29-2.09)	0.63	0.81 (0.30-2.19)	0.68
10	Simple Phobia	0.72 (0.45-1.16)	0.15	0.19	0.74 (0.47-1.16)	0.19	0.86 (0.54-1.36)	0.51
11	Opioid Dependence	0.58 (0.09-3.44)	0.50	0.49	0.59 (0.13-2.64)	0.49	1.05 (0.23-4.69)	0.95
	Column	01	02	03	04	05	06	07

Table C7P1T02 summarizes the estimates of several survival analyses techniques comparing the SERT (s) allele carrier with the non-carrier subgroups. Column 01 included the estimated the Ratio between the Incidence Rates of the two groups. Column 03 includes the results of the Log Rank tests comparing the survival curves of the two groups. Column 04 displays the results of the unadjusted Hazard Ratios for each disorder obtained from the Cox Proportional Hazards Regression Analyses. Column 06 summarizes the estimates of the Hazard Ratios, adjusted by gender, ethnicity, and marital status.

C07T03. Lifetime Use of Medications per 100 patients, in Whole Sample, Genotyped Sample, and by SERT (S) Carrier Status

Row	Medication Type	Whole Sample (n=847)	Genotyped Sample (n=628)	SERT Carrier (SS+LS) (n=348)	SERT Non-Carrier (LL)(n=280)	Carrier/ Non-Carrier	Sig
01	Any Psychotropic Medication Use	10.51	10.19	9.48	11.07	0.86	0.51
02	Anti-depressant or Anti-anxiety Medication Use	8.85	8.44	8.05	8.93	0.90	0.69
03	Anti-depressant Medication Use	6.14	5.73	5.46	6.07	0.90	0.74
04	Anti-Anxiety Medication Use	4.25	4.62	4.60	4.64	0.99	0.98
05	Hypnotic Medication Use	1.77	2.07	1.72	2.05	0.69	0.50
06	Anti-psychotic Medication Use	1.42	1.11	0.86	1.43	0.60	0.51
07	Anti-manic Medication Use	1.06	1.27	0.86	1.78	0.48	0.32
	Column	01	02	03	04	05	06

Table C7T03 summarizes the findings of our analyses on the use of psychotropic agents. Antidepressant agents were the most widely prescribed for our subjects (8.85 per 100 subjects), followed by anti-anxiety agents (4.25 per 100 subjects). The overall use of psychotropic agents in the sample (including all types of psychotropic medications) was equal to 10.51 per 100 subjects. No statistical significant association was found on the SERT (s) allele carrier status and the use of any psychotropic medications, considered individually or as a cumulative use.

TABLES FOR APPENDIX 02.

Table AP02T01. Diagnostic Counts of Selected Mental Disorders. Divided by Diagnostic Groups on Carriers SERT (s) Allele. (N=348)

Row		No Diag DG0	One Diag DG1	Two Diag DG2	Three Diag DG3	Four Diag DG4	Five Diag DG5	Six Diag DG6	Totals
01	Alcohol Dependence	0	27	26	13	5	2	0	73
02	Alcohol Abuse	0	12	5	4	1	1	0	23
03	Major Depressive DO	0	14	24	15	6	5	0	64
04	Bipolar Disorder	0	6	3	0	2	0	0	11
05	Psychotic Disorders	0	1	1	1	0	0	0	3
06	Panic Disorder	0	4	10	5	4	3	0	26
07	Agoraphobia	0	2	4	3	5	4	0	18
08	Social Phobia	0	5	14	13	7	5	0	44
09	Obsessive Comp DO	0	0	1	0	0	1	0	2
10	Generalized Anxiety DO	0	2	1	3	1	1	0	8
11	Anxiety Disorder NOS	0	3	3	1	0	0	0	7
12	Dysthymic Disorder	0	2	1	1	0	0	0	4
13	Depressive Disorder NOS	0	3	2	1	1	0	0	7
14	Simple Phobia	0	10	17	13	1	3	0	44
15	Adjust DO Dep Mood	0	6	5	3	0	0	0	14
16	Opioid Dependence	0	3	3	5	3	0	0	14
17	#Diagnoses Per Group DG	0	100	120	81	36	25	0	362
18	# Individuals Diagnosed	0	100	60	27	9	5	0	201
19	# Individuals per Group	147	100	60	27	9	5	0	348
	Column	01	02	03	04	05	06	07	08

Table AP02T01 details the diagnostic counts of the stratification of the 348 SERT (s) allele carrier subjects in the sample. Rows 01 through 15 display the number of diagnoses of each individual mental disorder. Column 01 displays the individuals that did not receive any psychiatric diagnosis. Columns 02 through 07, rows 01 through 16 display the number of subjects diagnosed with a mental disorder in each diagnostic group. The cells of column 08, rows 01 through 16 display the total number of diagnoses for the individual mental disorders. Row 17 contains the number of diagnoses accrued by each diagnostic group (DG0=0, DG1=100, DG2=120, DG3=81, DG4=36, DG5=25, and DG6=0) and by all carrier sub-sample (N=362). Row 18 displays the number of individuals that received a diagnosis in each group (DG0=0, DG1=100, DG2=60, DG3=27, DG4=9, DG5=5, and DG6=0) as well as in the SERT (s) allele carrier sub- sample (N=201). In columns 01 through 07, row 19 displays the number of individuals in each group (DG0=147, DG1=100, DG2=60, DG3=27, DG4=9, DG5=5, and DG6=0). In column 08, row 19 displays the individuals diagnosed in the total sample (N=348).

Table AP02T02. Diagnostic Counts of Selected Mental Disorders. Divided by Diagnostic Groups on Non-Carriers SERT (s) Allele. (N=280)

Row		No Diag DG0	One Diag DG1	Two Diag DG2	Three Diag DG3	Four Diag DG4	Five Diag DG5	Six Diag DG6	Totals
01	Alcohol Dependence	0	17	21	9	3	3	1	54
02	Alcohol Abuse	0	7	4	4	1	1	0	17
03	Major Depressive Disorder	0	17	19	13	2	2	1	54
04	Bipolar Disorder	0	1	1	1	0	1	0	4
05	Psychotic Disorders	0	0	1	2	0	0	0	3
06	Panic Disorder	0	1	2	5	0	0	0	8
07	Agoraphobia	0	3	4	6	2	3	1	19
08	Social Phobia	0	7	10	4	2	5	1	29
09	Obsessive Compulsive DO	0	0	0	1	2	3	0	6
10	Generalized Anxiety DO	0	3	1	2	3	1	0	10
11	Anxiety Disorder NOS	0	1	3	1	0	0	1	6
12	Dysthymic Disorder	0	0	2	0	1	1	0	4
13	Depressive Disorder NOS	0	2	3	1	0	0	1	7
14	Simple Phobia Disorder	0	15	14	9	2	5	0	45
15	Adjust DO Dep Mood	0	3	6	1	1	0	0	11
16	Opioid Dependence	0	5	1	4	1	0	0	11
17	#Diagnoses Per Group DG	0	82	92	63	20	25	6	288
18	# Individuals Diagnosed	0	82	46	21	5	5	1	160
19	# Individuals	120	82	46	21	5	5	1	280
	Column	01	02	03	04	05	06	07	08

Table AP02T02 details the diagnostic counts of the stratification of the 280 SERT (s) allele non-carrier subjects in the sample. Rows 01 through 15 display the number of diagnoses of each individual mental disorder. Column 01 displays the individuals that did not receive any psychiatric diagnosis. Columns 02 through 07, rows 01 through 16 display the number of subjects diagnosed with a mental disorder in each diagnostic group. The cells of column 08, rows 01 through 16, display the total number of diagnoses for the individual mental disorders in the whole non-carrier sub-sample. Row 17 contains the number of diagnoses accrued by each diagnostic group (DG0=0, DG1=82, DG2=92, DG3=63, DG4=20, DG5=25, and DG6=6) and by all non-carrier sub-sample (N=288). Row 18 displays the number of individuals that received a diagnosis in each group (DG0=0, DG1=82, DG2=46, DG3=21, DG4=5, DG5=5, and DG6=2) as well as in the non-carrier sub- sample (N=160). In columns 01 through 07, row 19 displays the number of individuals in each group ((DG0=120, DG1=82, DG2=46, DG3=21, DG4=5, DG5=5, and DG6=1). In column 08, row 19 displays the individuals diagnosed in the total sample (N=280).

Table AP02T03. Unadjusted and Adjusted Diagnostic Counts, and Ratios for Carriers of the SERT (s) Allele (N=348) and Non-Carriers (N=280)

Row		Carrier Adj Diag	Carrier Unadj Diag	Carrier DIR	Carrier SDIR	Non-Carrier Adj Diag	Non-Carrier Unadj Diag	Non-Carrier DIR	Non-Carrier SDIR	Ratio DIR Carrier /DIR Non Carrier
01	Alcohol Dependence	45.98	73	1.59	0.88	32.02	54	1.69	0.94	0.94
02	Alcohol Abuse	16.28	23	1.41	0.78	10.78	17	1.58	0.88	0.90
03	Major Dep DO	33.50	64	1.91	1.06	31.90	54	1.69	0.94	1.13
04	Bipolar Disorder	8.00	11	1.38	0.76	2.03	4	1.97	1.09	0.70
05	Psychotic DOs	1.83	3	1.64	0.91	1.17	3	2.57	1.43	0.64
06	Panic Disorder	12.27	26	2.12	1.18	3.67	8	2.18	1.21	0.97
07	Agoraphobia	7.05	18	2.55	1.42	8.27	19	2.30	1.28	1.11
08	Social Phobia	19.08	44	2.31	1.28	15.00	29	1.93	1.07	1.19
09	Obs Comp DO	0.70	2	2.86	1.59	1.43	6	4.19	2.33	0.68
10	Gen Anxiety DO	3.95	8	2.03	1.12	5.12	10	1.95	1.09	1.04
11	Anxiety DO NOS	4.83	7	1.45	0.80	3.00	6	2.00	1.11	0.72
12	Dysthymic DO	2.83	4	1.41	0.78	1.45	4	2.76	1.53	0.51
13	Dep DO NOS	4.58	7	1.53	0.85	4.00	7	1.75	0.97	0.87
14	Simple Phobia	23.68	44	1.86	1.03	26.50	45	1.70	0.94	1.09
15	Adj DO Dep Mood	9.50	14	1.47	0.82	6.58	11	1.67	0.93	0.88
16	Opioid Dependence	6.92	14	2.02	1.12	7.08	11	1.55	0.86	1.30
17	Totals	Carriers Total # Unadj Diag: 201	Carriers Total # Adjusted Diag: 362	Carrier Total Sample DIR: 1.80	Carrier SDIR: 1.00	Non-Carr Total # Unadj Diag: 160	Non-Carr Total # Adjusted Diag: 288	Non-Carr Total Sample DIR: 1.80	Non-Carrier SDIR: 1.00	Sample Ratio DIR Carrier/Non-Carrier: 1.00
	Column	01	02	03	04	05	06	07	08	09

Table AP02T03. Unadjusted and Adjusted Diagnostic Counts, and Ratios for Carriers of the SERT (s) Allele (N=348) and Non-Carriers (N=280). This table displays the result of the adjustment process and the resulting ratios. Column 01, row 01 through row 16 displays the number of adjusted diagnoses for each disorder for the carrier sample (N=348). Column 01, row 17, the total number of adjusted diagnoses in the carrier sample (201). Column 02, rows 01 through 16, displays the number of unadjusted diagnoses for each disorder in the carrier sub-sample. Column 02, row 17, the total number of unadjusted diagnoses in the carrier sub-sample (362). Column 03, rows 01 through 16, displays the Diagnostic Inflation Ratio (DIR) (Unadjusted # Diagnoses/ Adjusted # Diagnoses) for each disorder in the carrier sub-sample. Column 04, row 17, displays the DIR for the whole carrier sub-sample (1.80). Column 04, rows 01 through 16, displays the Standardized Diagnostic Inflation Ratio (SDIR) for each disorder (DIR of each disorder/ DIR whole carrier sub-sample). Column 05, row 01 through row 16 displays the number of adjusted diagnoses for each disorder for the non-carrier sub-sample (N=280). Column 05, row 17, the total number of adjusted diagnoses in the non-carrier sample (160). Column 06, rows 01 through 16, displays the number of unadjusted diagnoses for each disorder in the non-carrier sub-sample. Column 06, row 17, the total number of unadjusted diagnoses in the non-carrier sample (288). Column 07, rows 01 through 16, displays the Diagnostic Inflation Ratio (DIR) (Unadjusted # Diagnoses/ Adjusted # Diagnoses) for each disorder in the non-carrier sub-sample. Column 07, row 17, displays the DIR for the whole non-carrier sub-sample (1.80). Column 08, rows 01 through 16, displays the Standardized Diagnostic Inflation Ratio (SDIR) for each disorder in the non-carrier sub-sample (DIR of each disorder/ DIR whole non-carrier sub-sample). Column 09, rows 01 through 16 displays the ratio of the DIR of the carrier vs. the non-carrier sub-samples for each disorder. Column 09, row 17displays the ratio of the DIR of the whole carrier sub-sample versus the DIR of the whole non-carrier sub-sample.

Table AP02T04. Proportion Testing Between Carriers of the SERT (s) Allele (N=348) and Non-Carriers (N=280)

Row		Carrier Remaining Proportion After Adjustment	Non-Carrier Remaining Proportion After Adjustment	P- value Prop Testing
01	Alcohol Dep	0.63	0.59	0.67
02	Alcohol Abuse	0.71	0.63	0.62
03	Major Dep DO	0.52	0.59	0.46
04	Bipolar Disorder	0.73	0.51	0.43
05	Psychotic DOs	0.61	0.39	0.59
06	Panic Disorder	0.47	0.46	0.95
07	Agoraphobia	0.39	0.44	0.79
08	Social Phobia	0.43	0.52	0.48
09	Obs Comp DO	0.35	0.24	0.76
10	Gen Anxiety DO	0.49	0.51	0.94
11	Anxiety DO NOS	0.69	0.50	0.48
12	Dysthymic DO	0.71	0.36	0.33
13	Dep DO NOS	0.65	0.57	0.75
14	Simple Phobia	0.54	0.59	0.63
15	Adj DO Dep Mood	0.68	0.60	0.68
16	Opioid Dep	0.49	0.64	0.45
17	# Total	0.56	0.56	0.99
	Column	01	07	10

Table AP02T04 displays the proportion testing between the carrier sub-sample (N=348) and non-carrier sub-sample (N=280). Column 01 Rows 01 through 16 displays the proportion of the diagnostic information remaining after the adjustment process for each disorder in the carrier sub-sample (Remainder Proportion After adjustment process) Column 01 Row 17 the proportion of the diagnostic remaining after the adjustment for the whole carrier sub-sample. Column 02 displays diagnostic information remaining after the adjustment process for the non-carrier sub-sample. Column 03 displays the results of the two sample test for proportions between the carrier and non-carrier sub-samples.

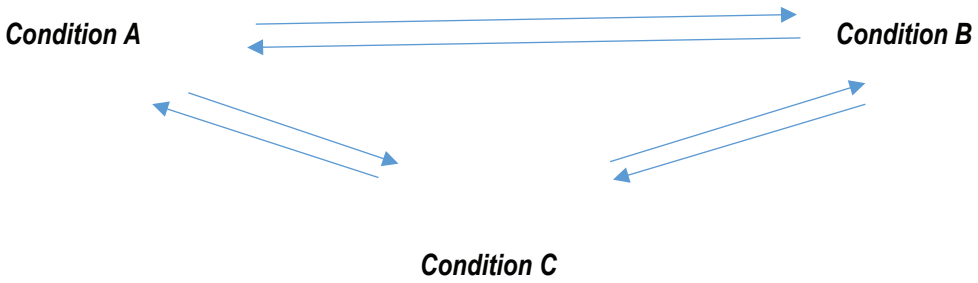
CHAPTER 06: FIGURES

Figure C6F01A. Example of Comorbidity Count on Individuals with Two Diagnoses

Total Number of Comorbidity Dyads or Pairs per Subject= 2

Total Number of Comorbidity Dyads or Pairs per Condition = 1

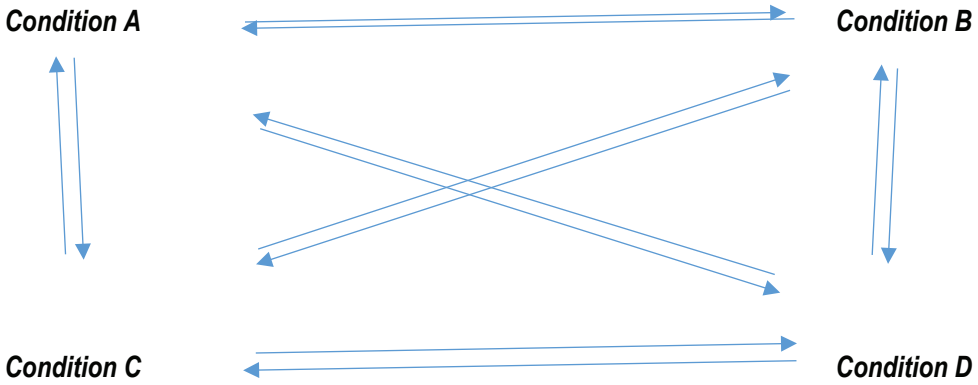
Figure C6F01B Example of Comorbidity Count on Individuals with Three Diagnoses.



Total Number of Comorbidity Dyads or Pairs per Subject = 6

Total Number of Comorbidity Dyads or Pairs per Condition = 2

Figure C6F01C. Example of Comorbidity Count on Individuals with Four Diagnoses.



Total Number of Comorbidity Dyads or Pairs per Subject = 12

Total Number of Comorbidity Dyads or Pairs per Condition = 3

Figure C6F02 Number of Diagnoses, Comorbidities and Individuals in Whole Sample by Diagnostic Group or Strata

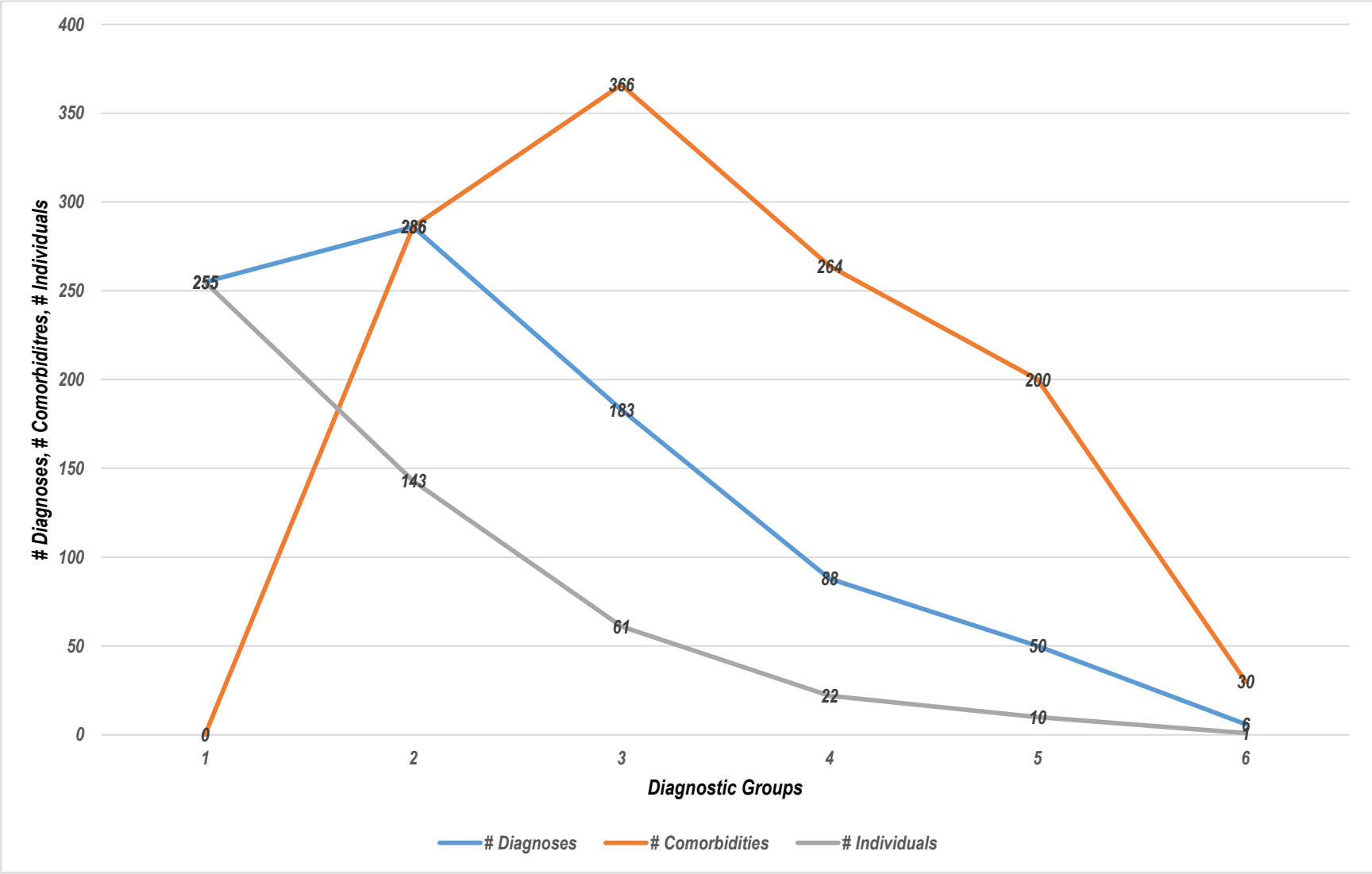


Figure C6F02 Shows the Distribution of the Number of Diagnoses (in blue), the number of comorbidities (in orange), and the number of Individuals (in grey) in the sample, stratified by Diagnostic Group or Strata

Figure C6F03 Relationship Number of Diagnoses/ Number of Comorbidities by Diagnostic Group

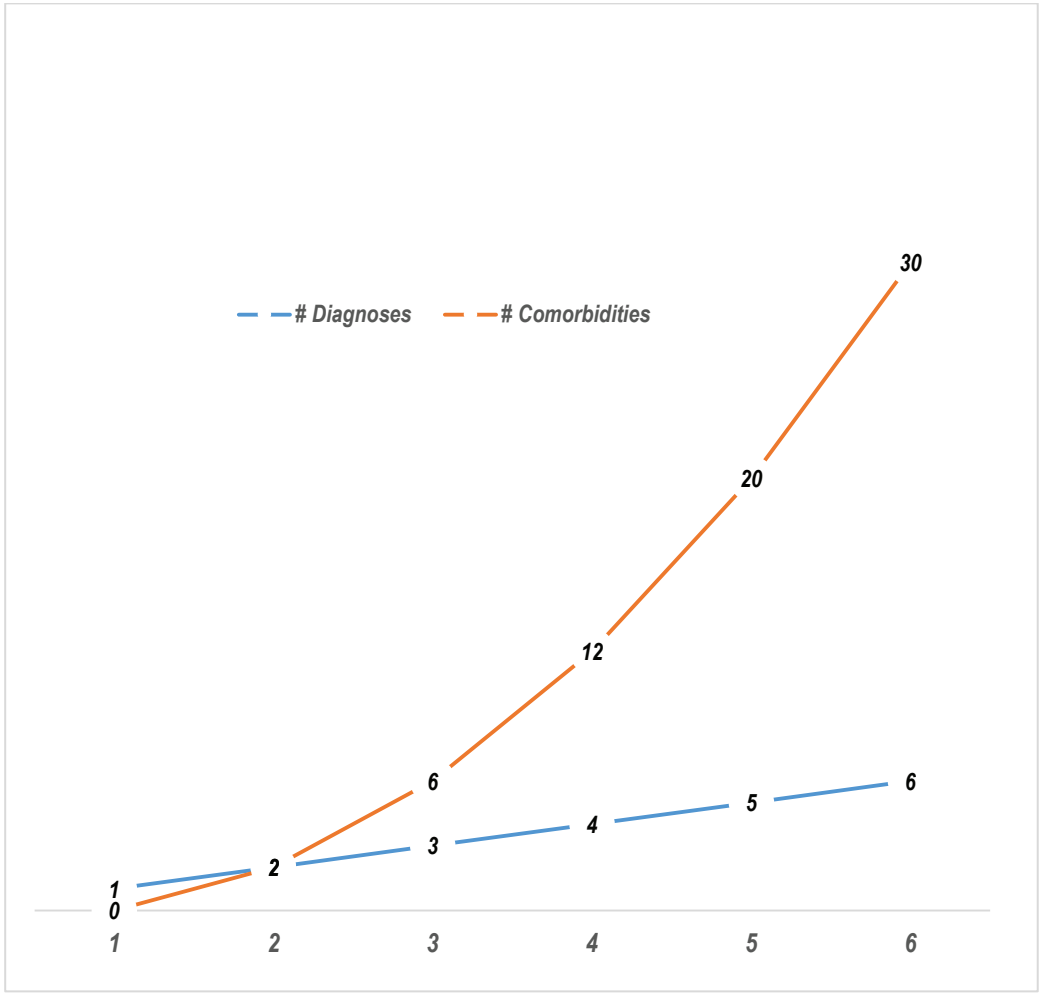


Figure C6F03 Displays the Relationship between the number of diagnoses and the number of comorbidities by Diagnostic Group or Stata

An Individual in the DG3 will have the following characteristics

 # Diagnoses= Modal Number of Diagnoses in the Diagnostic Group (MDDG) = 3

 # Comorbidities = (MDDG) (MDDG-1) =3 x 2 = 6

An individual in the DG5 will have the following characteristics

 # Diagnoses = Modal Number of Diagnoses in the Diagnostic Group (MDDG) = 5

 # Comorbidities = (MDDG) (MDDG-1) =5 x 4 = 20

CHAPTER 04: FIGURES

Figure C4AF01: Flow Diagram Study Participants Selection Process

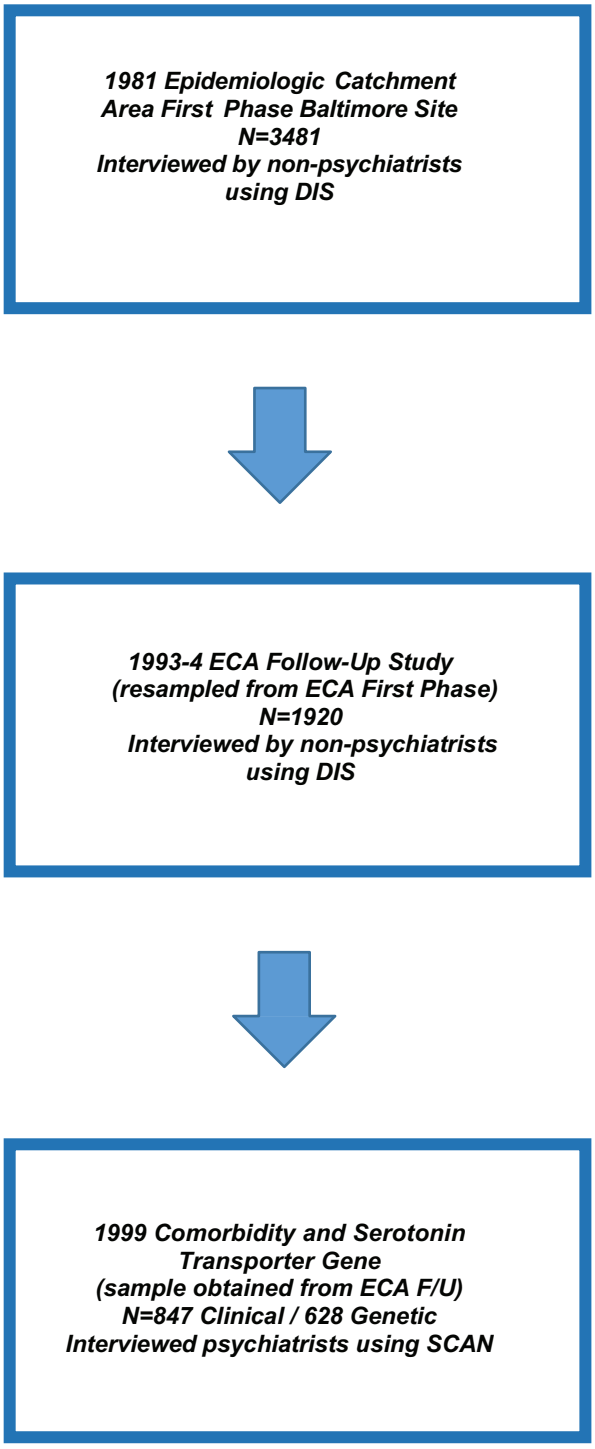


Figure C4AF01: Flow Diagram Study Participants Selection Process displays the three phase subject selection process. In 1981, a probabilistic sample of N=3481 Easter Baltimore residents was done for the original Epidemiologic Catchment Area (ECA). In 1993-4, a sample of N=1920 of the ECA participants was selected for ECA Baltimore Follow-up (EFU). In 1999, a sample of N=847 subjects of the original ECA and EFU was obtained for our study. These participants were interviewed by a psychiatrist using the SCAN. A sub-sample of N=628 provided genetic information.

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APPENDIX 01.

PROBABILITY CONCEPTS ON DIAGNOSES AND COMORBIDITIES IN A SAMPLE

AP1.Part 01. Summary on the Probability Distributions of the Total Number of Individuals Diagnosed, the Total Number of Diagnoses, and the Total Number of Comorbidities

AP1.P01.S01. Introduction, Aims and Rationale

As we mentioned in Chapter 06, the relationship between the Total Number of Individuals Diagnosed, the Total Number of Diagnoses, and the Total Number of Comorbidities can be understood as three different but related random probability distributions. These distributions share random elements that pertain to each sample analyzed, and fixed probabilistic elements that are particular to each distribution, and are universal to all samples.

The random elements include: 1) the number of diagnostic groups or strata that in probability terms translates as the number of possible outcomes in a random distribution; and, 2) the number of individuals in each diagnostic strata that in probability terms translates into the probability of each outcome (as proportions to the total number). As we have already mentioned, these elements are dependent on the particular sample that we are analyzing and are shared by the three distributions.

The fixed elements correspond to values attached to each outcome. These values are specific to each distribution and are permanent, regardless the samples under study. While the number of outcomes is contingent on the sample under examination, the values attached to each of these outcomes for these 3 distributions are a function that can be predicted.

In this analysis, we will demonstrate all the computations needed to obtain the values of these three distributions. These calculations will help to prove the mathematical basis of the Diagnostic Inflation Ratio, and the Comorbidity Inflation Ratio.

AP1.P01.S02 Definitions

DG: Diagnostic Group or Strata

DG0= Diagnostic Group Comprised by Individuals in the Sample that received no Axis I Disorder Diagnoses (Lifetime Prevalence).

DG1= Diagnostic Group Comprised by Individuals Diagnosed with One Axis I Disorder,

DG2= Diagnostic Group Comprised by Individuals Diagnosed with Two Axis I Disorders.

DGK= Diagnostic Group Individuals Diagnosed with the highest amount of diagnoses per individual in sample.

In our sample there are 7 diagnostic groups (6 with diagnosed individuals)

=> DG0+ DG1+ DG2+ DG3+ DG4+ DG5+ DG6. In our sample DGK=DG6

MDDG= Modal Number of Diagnoses by Diagnostic Group.

MDDG0=0, MDDG1=1, MDG2=2, MDGK=K

In our sample => MDDG0=0, MDDG1=1, MDDG2=2, MDG3=3, MDG4=4, MDG5=5 MDG6=6

NIG= Number of Individuals per Group

NI1G0= number of individuals in G0,

NI1G1= number of individuals in G1,

NIG2= Number of Individuals in G2,

NIGK= Number of Individuals in GK

In our sample (Table 03A (Row 19)) =>

NIDG0= 355, NIDG1= 255, NIDG2=143, NIDG3=61, NIDG4=22, NIDG5= 10, NIDG6=1

NTI =Number of Total individuals (Sample Size) = $\sum_{1=NIDG0}^{NIDGK}$

IN OUR SAMPLE (Table C6T003A (Row 19)) =>

NTI =NIDG0 + NIDG1 + NIDG2+ NIDG3+ NIDG4 + NIDG5 +NIDG6

NTI = 355 + 255 + 143 + 61 + 22 + 10 + 1 = 847

NTID =Number of Total individuals Diagnosed = $\sum_{1=NIDG1}^{NIDGK}$ *(excludes DG0 Individuals)*

IN OUR SAMPLE (Table C6T03A (Row 18)) =>

NTID = NIDG1 + NIDG2+ NIDG3+ NIDG4 + NIDG5 +NIDG6=

NTID = 255 + 143 + 61 + 22 + 10 + 1 = 492

PIDDG= Proportion of Individuals Diagnosed by Diagnostic Group (Excludes DG0)

PIDDG1= (NIDG1 / NTID) = Proportion of individuals in DG1 (also probability of DG1),

PIDDG2 = (NIDG2 / NTID) = Proportion of Individuals in DG2 (also probability of DG2),

PIDDGK= (NIDGK/ NTID) Proportion of Individuals in DGK (also Probability DGK)

In our Sample

PIDDG1 + PIDDG2 + PIDDG3 + PIDDG4 + PIDDG5 + PIDDG6 =1

0.51829 + 0.29065 + 0.12398 + 0.04472 + 0.02033 + 0.00203 = 1

Notes: This information is presented as percentages in Table C6T03B (Row 18). Proportion of each DG equals to the probability of one individual diagnosed in the sample to be a member of each DG. Addition of all possible probabilities equals to one

AP1.P01.S03. Values for Each Outcome in the Distribution of Total Number of Individuals Diagnosed

This can be obtained with a permutation that selects one diagnosis (r) at a time out of a set (n) that is defined by the modal of diagnoses of the diagnostic group. In this distribution we are allowing a MDDG=1 for every DG. It serves for the adjustment process, showing a counterfactual state where comorbidity does not exist or would not be permitted by the classification. In practical terms the value of each outcome will be always be 1.

Value Outcome Diagnostic Group= VODG = 1

$_nP_r = {}_1P_1$ *for all groups = For DG1=>* $VODG1 = {}_1P_1 = 1$,

For DG2=> $VODG2 = {}_1P_1 = 1$,

For DGK=> $VODGK = {}_1P_1 = 1$

AP1.P01.S04. Values for Each Outcome in the Distribution of Total Number of Diagnoses

This can be obtained with a permutation that selects one diagnosis (r) at a time out of a set (n) that is defined by the modal of diagnoses of the diagnostic group. In this distribution we are allowing a MDDG to grow in each DG. In practical terms, the result of the permutation will be identical to the modal diagnoses of each diagnostic group. This is tautological, as we have selected the DG based on the number of diagnoses

Value Outcome Diagnostic Group= VODG= MDDG

$_{n}P_{r} = {}_{MDDG}P_{1}$ *for all groups = For DG1=> VODG1=* $_{MDDG1}P_{1} = 1$,

$$\text{For DG2=> VODG2} = {}_{MDDG2}P_{1} = 2,$$

$$\text{For DGK=> VODGK} = {}_{MDDGK}P_{1} = K$$

⇨ *VODG= Modal Number of Diagnoses of the Diagnostic Group*

AP1.P01.S05. Values for Each Outcome in the Distribution of Total Number of Comorbidities

This can be obtained with a permutation that selects two diagnoses (r) at a time out of a set (n) that is defined by the modal of diagnoses of the DG. As we are counting comorbidities, there is a need to select 2 diagnoses at a time. In practical terms this will be identical as the value of each outcome will be the product of the (MDDG) (MDDG-1)*

Value Outcome Diagnostic Group= VODG = (MDDG) (MDDG-1)*

$_{n}P_{r} = {}_{MDDG}P_{2}$ *for all groups = For DG1=> VODG1=* $_{MDDG1}P_{2} = 0$,

$$\text{For DG2=> VODG2} = {}_{MDDG2}P_{2} = 2$$

$$\text{For DGK=> VODGK} = {}_{MDDGK}P_{2} = (K)*(K-1)$$

AP1.P01.S06. Expected Value for Total Number of Individuals Diagnosed:

The expected value represents the average of all outcomes. It is obtained by the addition of the product of probability of each outcome (or better said, the proportion of individuals diagnosed by DG) by the value of each outcome of the distribution. In this distribution, the value of all outcomes is 1. Each product will be equal to the probability of each DG. The sum of all probabilities will be equal to 1

$$\sum_{i=G1}^{K} PIDG * VODG$$

*(PIDDG1 *VODG1) + (PIDDG2 *VODG2) + (PIDDG3 *VODG3) + (PIDDG4 *VODG4) + (PIDDG5 *VODG5) + (PIDDG6 *VODG6) =*

=0.51829 1 + 0.29065 *1 + 0.12398 *1 + 0.04472*1 + 0.02033*1 + 0.00204*1 = 1*

AP1.P01.S07. Expected Value for Total Number of Diagnoses

In this distribution, the value of all outcomes went from 1 through K. The expected value will represent the average value of all outcomes, or, better said, the average number of diagnoses per individual. This is none other than the Diagnostic Inflation Index

$$\sum_{i=G1}^{K} PIDG * VODG$$

*(PIDDG1 *VODG1) + (PIDDG2 *VODG2) + (PIDDG3 *VODG3) + (PIDDG4 *VODG4) + (PIDDG5 *VODG5) + (PIDDG6 *VODG6) =*

=0.518292683 1 + 0.290650407 *2 + 0.12398374 *3 + 0.044715447 *4 + 0.020325203*5 + 0.00203252*6 = 1.764227642*

Expected Value for Total Number of Diagnoses = DIR = 1.76

The added advantage is that we can obtain a variance of this expected value that will allow to make better inferences

Variance= $\sum(PIDG * VODG)^2 - Expected\ Value^2$

Variance= 0.86937492 -> Standard Deviation= 0.932402767= 0.93

AP1.P01.S08. Expected Value for Total Number of Comorbidities

In this distribution, the value of all outcomes went from 0 through (K)(K-1). The expected value will represent the average value of comorbidities per individual diagnosed. The result is identical to the Comorbidity Inflation Ratio*

$$\sum_{i=G1}^{K} PIDG * VODG$$

*(PIDDG1 *VODG1) + (PIDDG2 *VODG2) + (PIDDG3 *VODG3) + (PIDDG4 *VODG4) + (PIDDG5 *VODG5) + (PIDDG6 *VODG6) =*

=0.518292683 0 + 0.290650407 *2 + 0.12398374 *6 + 0.044715447 *12 + 0.020325203*20 + 0.00203252*30 =2.329268293*

Expected Value for Total Number of Comorbidities = CIR = 2.33

APPENDIX 01. PROBABILITY CONCEPTS

AP1.Part 02. Summary on the Probability Distribution for the Comorbidity to Inflation Ratio

AP1.P02.S01. Introduction, Aims and Rationale

The previous probability distributions that we calculated in Part 01 helped to demonstrate the mathematical basis of the DIR, and the CIR. These distributions represent the expected value of diagnoses or comorbidities per individual diagnosed. These distributions are therefore based in a ratio of diagnoses and comorbidities to individuals diagnosed.

In contrast, the Comorbidity to Inflation Ratio (CDIR) represents the ratio of comorbidities to diagnoses. In order to obtain the CDIR by a random probability distribution, we must have stratified the number of diagnoses per diagnostic group (as we did in Table 03A, Row 17). This distribution has, as those previously discussed, two random elements: 1) the number of possible outcomes that is comprised by the number of diagnostic groups of the sample, and 2) the probability of each possible outcome. These probabilities are obtained by calculating the proportion of diagnoses in each DG to the total number of Diagnoses. These random elements are particular of the sample under examination.

The fixed element of the distribution is the value of each outcome. This is obtained by calculating the ratio between the values of the outcomes of the Expected Comorbidity and the values of the outcomes of the Expected Diagnosis for each DG. The value of each outcome will be done by the ratio of permutations of the two previous distributions (as we are doing a ratio of

comorbidities to diagnoses). This ratio will always yield the same value in each diagnostic group as expected value. This value will be the MDDG-1.

AP1.P02.S02. Elements of the Distribution of the Comorbidity to Diagnosis Inflation Ratio (CDIR)

NDG= Number of Diagnoses per Group

NDG0= Number of Diagnoses in G0,

NDG1= Number of Diagnoses in G1,

NDG2= Number of Diagnoses in G2,

NIGK= Number of Diagnoses in GK

In our sample (Table C03A, Row 17) =>

NDDG0= 0, NDDG1= 255, NDDG2=286, NDDG3=183, NDDG4=88, NDDG5= 50, NDDG6=6

NTD =Number of Total Diagnoses = $\sum_{1=NIDG0}^{NIDGK}$

IN OUR SAMPLE =

NTD= NDDG0 + NDDG1 + NDDG2+ NDDG3+ NDDG4 + NDDG5 +NDDG6=

NTD = 0 + 255 + 286 +183 + 88 + 50 + 6 = 868

PDDG= Proportion of s Diagnosed by Diagnostic Group (Excluded DG0)

PDDG1= (NDDG1 / NTD) = Proportion of Diagnoses in DG1 (also probability of DG1),

PDDG2 = (NDDG2 / NTD) = Proportion of Diagnoses in DG2 (also probability of DG2),

PDDGK= (NDDGK/ NTD) Proportion of Diagnoses in DGK (also Probability DGK)

In our Sample

PDDG1 + PDDG2 + PDDG3 + PDDG4 + PDDG5 + PDDG6 =1

0.29378 + 0.32949 + 0.21083 + 0.10138 + 0.05760 + 0.00691 = 1

Notes: This information is presented as percentages in Table C6T03B (Row 17). Proportion of each DG equals to the probability of any diagnosis picked up at random to will belong to any diagnostic group. The addition of all possible probabilities in the sample space equals to one

<u>AP1.P02.S03. Values for Each Outcome in the Distribution of the Ratio of Comorbidity to Diagnoses</u>

As mentioned above the Value of the Outcome for this distribution is the ratio between the values of the outcomes of the Expected Comorbidity and the values of the outcomes of the Expected Diagnosis for each DG. In practical terms the value of each outcome will be always be MDDG-1 for each DG

Value Outcome Diagnostic Group= VODG = MDDG-1

$_{n}P_{r} = {}_{MDDG}P_{2} / {}_{MDDG}P_{1} = (MDDG) \times (MDDG-1) / MDDG = (MDDG-1)$

For all groups = For DG1=> VODG1= $_{MDDG1}P_{2} / {}_{MDDG1}P_{1} = 0$

For DG2=> VODG2= $_{MDDG2}P_2$ / $_{MDDG2}P_1$ = 1

For DG3=> VODG3= $_{MDDG3}P_2$ / $_{MDDG3}P_1$ = 2

For DGK=> VODGK= $_{MDDGK}P_2$ /$_{MDDGK}P_1$ = (K-1)

AP1.P02. S04. Expected Value for Comorbidity to Diagnosis Ratio

The expected value will represent the average value of comorbidities per diagnosis. The result is identical to the Comorbidity to Diagnosis Inflation Ratio (CDIR). The CDIR can also be defined as the ratio between the CIR and the DIR (2.32 / 1.764)

$$\sum_{i=G1}^{K} PDDG * VODG$$

*(PDDG1 *VODG1) + (PDDG2 *VODG2) + (PDDG3 *VODG3) + (PDDG4 *VODG4) + (PDDG5 *VODG5) + (PDDG6 *VODG6) =*

*= 0.293778802 * 0 + 0.329493088 *1 + 0.210829493*2 + 0.101382488*3 +*

*0.057603687*4 + 0.006912442 *5 = 1.320276498=*

= 1.320276498

Expected Value for Comorbidity to Diagnosis Ratio (CDIR) = 1.32

Variance= $\sum(PIDG * VODG)^2 - Expected\ Value^2$

Variance = 1.436593472 -> Standard Deviation = 1.198579773 = 1.2

APPENDIX 02. ADJUSTMENT METHODS

AND SEROTONIN TRANSPORTER GENE POLYMORPHISM.

AP02.S01. Aims

In this appendix, we will display the results of the adjustment process when used to compare the comorbidity burden between two samples.

In this case, we will be using the adjustment process to compare the comorbidity burden between the participants who were carriers of the Serotonin Transporter Gene Short (s) Polymorphism (N=348) and those participants who were non-carriers for the same allele (N=280).

AP02.S02. Stratification and Adjustment

Table AP02T01 details the diagnostic counts of the stratification of the 348 SERT (s) allele carrier subjects in the sample. Table AP02T02 details the diagnostic counts of the stratification of the 280 SERT (s) allele non-carrier subjects in the sample.

Table AP02T03 displays the result of the adjustment process and the resulting ratios. The carrier and the non-carrier subsample had nearly identical Diagnostic Inflation Ratio for the total sub-sample (1.80). This indicates, that the comorbidity burden was not associated in study with the SERT polymorphism, as considered globally

The analysis of any differential comorbidity burden between the carrier and the non-carrier subsamples for the individual disorders was hindered by a relatively small sample size.

In table AP02T03, we calculated a ratio between the DIR of the carrier sub-sample and the DIR of the non-carrier sub-sample. Dysthymic Disorder (DIR Ratio= 0.51), Schizophrenia and Other Psychotic Disorders (DIR Ratio: 0.64), were the conditions that had DIR ratios that appear diverse between carriers and non-carriers

AP02.S03. Proportion Testing

We calculated a 2 sample proportion testing for each condition as well as for the sub-samples as a whole to determine if there were any differences in the comorbidity burden of each sub-sample. Table AP02T04 displays the proportion testing between the carrier sub-sample and non-carrier sub-sample. The analysis yielded no statistically significant differences for the comorbidity burden between the carriers and non-carriers

APPENDIX 03: PSYCHIATRIC COMORBIDITY, ANTIPSYCHOTIC POLYPHARMACY, AND METABOLIC SYNDROME IN A LONG-TERM PSYCHIATRIC HOSPITAL POPULATION

AP3.S01. Introduction:

Pharmacological treatment of patients with severe mental illness remains a challenging task. The use of two or more antipsychotic (AP) agents, also called "antipsychotic polypharmacy" (APP), has been a common practice in spite of limited evidence on its efficacy (APR01-4).

The prevalence of APP varies widely by country. In the US, approximately 19.6% of all patients receiving AP therapy receive more than one AP agent (AP3R05). Compared to AP monotherapy, APP has been associated with increased hospitalization rates and length of stay (AP3R06-7), increased costs (AP3R08-9), as well as increased incidence of side effects (AP3R10). In particular, APP has been associated with an increased incidence of metabolic and cardiovascular side effects (AP3R06, AP3R10).

APP is a strategy that is commonly used to address poor treatment response to AP monotherapy. In some cases, lack of response to AP monotherapy in a patient is the result of the presence of comorbid mental disorders: namely, the presence of other mental disorders in addition to the diagnoses of Schizophrenia or Schizoaffective Disorder.

Patients with treatment resistant Schizophrenia or Schizoaffective Disorder are frequently inpatients in long-term psychiatric facilities. Most recent literature on psychopharmacology in state psychiatric facilities has focused on whether the results of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study (AP3R11-12) had an

impact in the AP agent of choice (AP3R13-14). Other important areas of research have been AP dosing and its relationship with ethnicity (AP3R15), and the adherence to treatment algorithms (AP3R16).

There is limited information about the prevalence of psychiatric comorbidity in patients at state psychiatric facilities and the effect of this comorbidity in AP prescribing practices. As AP prescription practices, in particular APP, can have an impact on the incidence of side effects, an examination of the relationship between diagnoses, AP prescriptions, and side effects is of crucial importance.

AP3.S02. Aims:

To explore the prevalence and pattern of psychiatric comorbidity (presence of more than one mental disorder diagnosis in the same individual) in a cohort of patients in a long-term psychiatric hospital. We will focus on the prevalence of the psychiatric comorbidity of Schizophrenia and Schizoaffective Disorder with substance abuse disorders.

To determine prescription patterns of AP agents, in particular the prevalence of antipsychotic polypharmacy (APP), and its association, with the presence of comorbidity in Schizophrenia and Schizoaffective Disorder.

To examine the association between the prevalence of metabolic side effects both with psychiatric comorbidity and with APP. In particular, we will examine the prevalence of hyperlipidemia, hyperglycemia, and increased body mass index (BMI) in patients who are receiving APP and have been diagnosed with Schizophrenia/ Schizoaffective Disorder comorbid with a substance abuse disorder.

AP3.S03. Methods: Study Sample:

: *Clinical data from 224 adult inpatients in a long term state psychiatric facility in Central Massachusetts during 2015 was gathered in a 2-month period. These 224 subjects were the total adult inpatient population of said hospital during that period.*

We reviewed electronic medical records and collected information on: age, sex, ethnicity, admission date, body mass index, primary diagnosis, legal status (voluntary versus involuntary).

We obtained data on psychotropic agent use by patient based on hospital pharmacy records. We obtained laboratory results from chart review including serum glucose level, glycosylated Hemoglobin (HGBA1C), plasma total cholesterol, plasma high density lipoprotein cholesterol (HDL), low density lipoprotein cholesterol (LDL), and plasma Triglyceride levels (TG)

AP3.S04. Methods: Definition of Metabolic Syndrome:

We defined metabolic syndrome combining criteria of current established guidelines (AP3R011-13). We identified metabolic syndrome in our sample by the presence of the following indicators: plasma triglyceride levels >150 mg/dl, plasma high density lipoprotein (HDL) levels < 40 mg/dl in males and < 50 mg/dl in females, fasting serum glucose level >100 mg/dl, body mass index (BMI) >30 kg/m2, and, hemoglobin A1C > 5.7% (AP3T16).

AP3.S05. Methods: Analytical Approach:

We examined the prevalence of Schizophrenia, Bipolar Disorder, Major Depressive Disorder, Anxiety Disorders, Substance Abuse Disorders, Personality Disorders, and Dementia and Other Organic Mental Disorders in the study sample.

We estimated the prevalence of comorbidity between the above listed disorders using analytical methods derived from the analysis of random probability distributions. These methods examined the relationship between the number of individuals diagnosed, the number of diagnoses and the number of comorbidities, and enabled us to measure the burden of comorbidity for each individual disorder as well as for the whole study population.

We described the prescription patterns for AP agents using an analytical approach that was similar to the one used for exploring diagnostic comorbidity. This approach enabled us to determine the extent of polypharmacy for each AP agent as well as for the whole study population.

Using univariate statistics (chi^2 and Fisher's Exact Test) we examined the association between Schizophrenia comorbid with Substance Abuse disorder with the use of AP, as well as with the presence of indicators of metabolic side effects (detailed above).

Using univariate statistics (chi^2 and Fisher's Exact Test) we examined the association between APP with the presence of indicators of metabolic side effects (detailed above)

AP3.S06. Results: Patients' Characteristics:

In our sample of 224 adult inpatients, mean age was 40.24 years, Male/Female ratio was 66.5/33.5%, 65.18% of the sample was white, and 44.64% was obese (Body Mass Index >= 30 kg/m^2) (AP3T01 and AP3T02).

AP3.S07. Results: Prevalence of Individual Psychiatric Disorders (as proportions to the whole sample of 224 patients)

Schizophrenia and Other Psychotic Disorders 0.72 (42.6% as a single diagnosis), Bipolar Disorder 0.10 (13.6% as a single diagnosis), Depression 0.11 (20% as a single diagnosis), Anxiety Disorders 0.03 (14.3% as a single diagnosis), Substance Abuse Disorders 0.45 (5.0% as a single diagnosis), Personality Disorders 0.13 (10.7% as a single diagnoses, and finally, Dementia and Organic Mental Disorders 0.09 (20% as a single diagnosis) (AP3T03, (AP3T06B).

AP3.S08. Results: Comorbidities of Schizophrenia:

Of the 162 patients diagnosed with Schizophrenia or Schizoaffective Disorder, 6.17% had diagnosed comorbid depression, and 43.21% had a comorbid Substance Abuse Disorder, respectively (AP3T04).

AP3.S08. Results: Burden of Comorbidity in the Whole Sample:

In order to perform a comprehensive analysis of the comorbidity pattern in our study population, we performed a ratio of the number of diagnoses and number of comorbidities for the whole sample and for each diagnoses. Table AP3T05 presents the result of the tally of the number of comorbidities and diagnoses for the whole sample and for each disorder. For the whole sample (AP3T05 Colum 08), there were 364 diagnoses and 342 comorbidities tallied. This translated into a Comorbidity to Diagnoses Ratio (CDIR) of 0.94 (94 comorbidities per 100 diagnoses in the whole sample). This limited CDIR might be explained by the aggregation of multiple diagnoses into one category (e.g. all the individual anxiety disorders were aggregated into one diagnostic category). Another factor that might explain the limited number of comorbidities in our study population is the reliance on service data for diagnostic information (as opposed to a comprehensive diagnosis from a validated scale).

AP3.S09. Results: Burden of Comorbidity of the Individual Psychiatric Disorders. The Comorbidity to Diagnosis Ratio:

Anxiety, Depressive, Personality and Substance Abuse Disorders were the most comorbid condition in the sample (AP3T05) as evidenced by high Comorbidity to Diagnoses Inflation Ratio (CDIR). Anxiety Disorders CDIR: 1.43, Personality Disorders CDIR: 1.32, Depressive Disorders CDIR: 1.16, and Substance Abuse Disorders CDIR: 1.15. This meant a ratio for Anxiety Disorders of 143 comorbidities per 100 diagnoses. We later standardized the CDIR using the CDIR of the whole sample as a denominator. As an example, the Standardized CDIR of Anxiety Disorders yielded a value of 1.52. This meant that Anxiety Disorders have comorbidity burden that was 52% times higher than the one of the whole sample. Schizophrenia/ Schizoaffective Disorder were the least comorbid conditions in the sample (CDIR: 0.64, SCDIR: 0.68). This is largely explained by the fact these disorders were the primary diagnoses on a large proportion of cases, as well as likely reason for admission (and therefore for the selection to the sample). The other psychiatric conditions were most likely secondary diagnoses, added later in time to the medical record.

AP3.S10. Results: Stratification of Patients According to the Number of Diagnosed Psychiatric Disorders:

We stratified the patients according to the number of diagnoses they had received. This enabled us to examine the relationship between the number of diagnoses, the number of individuals diagnosed and the number of individuals in the sample. In Table AP3T06A, Column 06, displays the findings. Of the 224 total individuals in the sample (Row 10), there were 216 individuals diagnosed (Row 09). These individuals contributed with 364 diagnoses (Row 08).

The highest number of diagnoses per patient was four (Table AP3T06A). We stratified the number of diagnoses of each disorder and of the total sample according to the number of diagnoses that the individuals received. We labeled these strata as diagnostic group (DG). As an example, if a patient had been diagnosed with 3 conditions (schizophrenia, an anxiety and a substance abuse disorder), this patient, as well as these 3 diagnoses were tallied in the diagnostic group 03)

AP3.S11. Results: Comorbidity in the Whole Sample: Association of Individuals Diagnosed and Number of Diagnoses

We analyzed the prevalence of diagnoses per patient. (Table AP3T06B, Row 09). A small proportion (0.036) of the inpatients had no diagnoses (corresponding to new admissions), 0.401 had one diagnoses, 0.469 had 2 diagnoses, 0.089 had 3 diagnoses, and 0.004 of the sample had 4 diagnoses. In row 08, column 02 of Table AP3T06B, we can see that only 0.247 (25%) of all diagnoses belong to patients without comorbidities. In this limited sample of patients with severe and persistent mental illness, the source of 75% of the diagnostic information originated from is from patients with multiple psychiatric diagnoses. These patients with comorbid conditions corresponded to 56% of the total sample.

AP3.S12. Results: Measurement of Comorbidity of Individual Disorders: The Diagnostic Inflation Ratio:

In order to measure the burden of comorbidity for the total as well as for the individual disorders, we devised a method that included two steps. The first step consisted in adjusting the number of diagnoses to the number of individuals diagnosed. This meant that if a patient had 2 diagnoses, each diagnosis would be divided by 2 in the adjustment process. The second step

consisted in obtaining a ratio between the original unadjusted diagnostic information and the estimates obtained in the adjustment step. We call this ratio the Diagnostic Inflation Ratio (DIR). We can also standardized the DIR of each disorder by the DIR estimate of the whole sample to detect the disorders that have a lower or higher comorbidity burden in the sample. The Diagnostic Inflation Ratio (DIR) (the ratio of diagnoses to individuals diagnosed) was 1.69 for the whole sample (Table AP3T07: Row 08, Col 04). The DIR for the whole sample is, in probability terms, the mean number of diagnoses to be expected from any individual diagnosed (DG01-DG-4) picked up at random. We can see that the DIR of the Anxiety Disorders is 2.05, of the Substance Abuse Disorders is 2.03, and of the Personality Disorders is 2.06. This means that, if we picked at random an individual diagnosed with any of these conditions, we can expect them to have a higher expected number of diagnoses. By standardizing the DIR of each disorder with the DIR estimate of the whole sample, we can clearly detect the conditions that have a burden of comorbidity that is higher or lower than the whole sample. Schizophrenia and Schizoaffective Disorder had a SDIR of 0.85 (15% less burden of comorbidity than the total sample), while Anxiety, Substance Abuse, And Personality Disorder had a SDIR that was 20% higher than the total sample.

AP3.S13. Results: The Comorbidity Inflation Ratio

The same method described above for the DIR can be done for the comorbidity tallies, both for the whole sample as well as for each individual disorder. The ratio of comorbidity count to diagnosed individuals can be called Comorbidity Inflation Ratio (CIR). For the whole sample the CIR was 3.27 (Table AP3T07: Row 08, Column 07). In probability terms, this is the expected or mean number of comorbidities in any diagnosed individual picked up at random. In contrast, if we condition this to an individual diagnosed with Anxiety Disorders, the expected number of comorbidities would be 4.98 (Table AP3T06: Row 04, Column 07). If we standardize the DIR of

the individual disorders with the one of the whole sample, we can see that the Standardized DIR of Anxiety Disorders was 1.52. This represents a comorbidity burden that is 52% higher than the total sample

AP3.S14. Results: Significance Tests for the Comorbidity of the Individual Disorders:

Table AP3T08 presents the results of the Chi Square and Fisher Exact Tests analysis of the diagnostic data stratified in diagnostic groups. Using these techniques, we were able to examine if any of the individual disorders deviated significantly from the distribution of the diagnoses across the diagnostic group or the total number of diagnoses. Substance Abuse Disorders, Personality Disorder, and Schizophrenia deviated significantly from the whole sample as to the number of diagnoses in each diagnostic strata

AP3.S15. Results: Use of Antidepressant and Mood Stabilizer Agents

The most used antidepressant agent in our study population was Trazodone with 45 prescriptions (that included antidepressant and hypnotic indications). Citalopram with 18 prescriptions, followed by Mirtazapine with 16 prescriptions, and Fluoxetine and Sertraline with 15 prescriptions followed (Table AP3T09). Valproate was the most prescribed mood stabilizer with 49 prescriptions. Lithium was the second most prescribed mood stabilizers with 23 prescriptions (Table AP3T10)

AP3.S16. Results: Use of Antipsychotic Agents

Olanzapine was the most widely used antipsychotic with 52 prescriptions (only oral formulation) (Table AP3T11). Mean dose of Olanzapine was 20 mg per day. Risperidone was

the second most widely prescribed antipsychotic agent. Risperidone oral formulations were received by 47 patients with a mean dose of 4.88 mg. Risperidone Long Term Injectable (LTI) formulations were received by 5 patients at a mean dose of 95.83mg per month. Overall, 50 patients received Risperidone in all formulations. Haloperidol was the only typical antipsychotic agent that had a robust presence. The oral formulations of Haloperidol were received by 35 patients with a mean dose of 15.57 mg per day. Haloperidol LTI formulations were received by 17 patients in the sample with a mean sample of 145.7 mg per month (Table AP3T11).

AP3.S17. Results: Use of Multiple Antipsychotic Agents:

Table AP3T12 presents the results of the analysis of AP polypharmacy in the sample. The analytic approach was similar to the one used to measure comorbidity. We tallied the number of prescriptions for each antipsychotic agent, as well as the cases in which patients received a concomitant AP prescription. In table AP3T12, row 03 column 05, we can see that 6 patients that received Clozapine also received Haloperidol. There were 276 prescriptions of antipsychotic agents (Row 16, Col 15). These primary prescriptions were associated with 186 concomitant prescriptions for an additional antipsychotic agent (Row 15, Col 15). This resulted in Primary to Concomitant Prescription Ratio for AP Use of 0.64 for the whole sample. This translates into positing that in 64% of the cases, a primary prescription for an antipsychotic was accompanied by an additional prescription for a different antipsychotic agent. After standardizing this ratio by the one of the whole sample, we can see that Loxapine, Chlorpromazine, Thiothixene, and Lusaridone were used in an additional antipsychotic agents at rates that nearly doubled the one of the whole sample.

AP3.S18. Results: Measures of Impact of Antipsychotic Use in the Sample:

Tables AP3T13 and AP3T17 indicate that 87% (194 out of the total 224) of the patients in the sample received at least one antipsychotic agent, and 32% of the patients (72 out of the total 224) received at least 2 antipsychotic agents. Atypical antipsychotic agents were widely used over the typical agents, as 0.73% of the sample received atypical antipsychotic agents. 82 patients (42% of those receiving any AP agent) received a mood stabilizer simultaneously, while 70 patients (36% of those receiving any AP agent) received an antidepressant (Table AP3T15).

AP3.S19. Results: Measurement of the Polypharmacy Burden:

In order to measure the burden of AP polypharmacy for the whole sample as well as for the individual AP agents, we used a similar approach than the used in the measurement of comorbidity. The results of the analysis can be seen in Table AP3T19. This method consisted of two steps. In the he first step, we adjusted the number of prescriptions to the number of individuals receiving and AP agent. This meant that if a patient had 2 AP prescriptions, each prescription would be counted as half. The second step of the method entailed the estimation of a ratio between the original prescription information and the adjusted estimates. We called this the Polypharmacy Ratio (PR). We also standardized the PR of each AP agent by the PR estimate of the whole sample to detect the AP agents that had a lower or higher polypharmacy burden than the whole sample. The Polypharmacy Ratio (PR) (the ratio of prescriptions to individuals prescribed) was 1.42 for the whole sample (Row 15, Col 04). The PR for the whole sample is, in probability terms, the mean number of AP prescriptions to be to be expected to find in any individual receiving an AP agent (PG1-PG4), randomly selected. We can see that the PR of lusaridone is 2.00, , the PR of loxapine is 1.85, the PR of chlorpromazine is 1.78, and the PR of fluphenazine is 1.78. This means that if we select at random an individual receiving any of these AP agents, we can expect this individual to be receiving a higher number of AP agents as compared to an individual receiving an alternate AP. By standardizing the PR of each AP

agent with the one of the whole sample, we can clearly detect the AP agents that have a polypharmacy burden that is higher or lower than the estimated for the whole sample. As an example, chlorpromazine and fluphenazine had an estimated SPR of 1.25. These estimates indicate that these AP agents have a 25% higher polypharmacy burden than the overall sample.

AP3.S20. Results: Use of Multiple Antipsychotic Agents and Comorbidity of Schizophrenia/ Schizoaffective Disorder with Substance Abuse

Our findings suggest that there was a positive association between having a diagnosis of Schizophrenia/ Schizoaffective Disorder comorbid with Substance Abuse and being prescribed one or more AP agent, as compared to non-comorbid patients with Schizophrenia/ Schizoaffective Disorder (Table AP3T22). We found no statistically significant association between the use of two or more antipsychotics with the comorbidities of schizophrenia (substance abuse and depression), and patient's sex, age, and overweight status (Table AP3T22).

AP3.S21. Results: Association between Metabolic Syndrome, Schizophrenia Comorbidity, and AP Polypharmacy

We were unable to find an association between the metabolic syndrome indicators and the presence of comorbidity of Schizophrenia/ Schizoaffective Disorder with Substance Abuse (Table AP3T20). We were unable to find any association between the metabolic syndrome indicators with the use of two or more AP agents (Table AP3T21).

AP3.S22. Conclusions. Strengths:

Our findings, although hindered by the relatively small sample size, are relevant in exploring diagnostic and AP prescribing patterns, as well as the prevalence of APP in long-term psychiatric hospitals and their association with the metabolic side effects. This study is particularly relevant due to the limited data on prescribing practices in this vulnerable population.

AP3.S23. Conclusions. Limitations:

The sample size was relatively small. The multiple analysis originated from a cross-sectional examination on the demographic, diagnostic, and pharmacologic data. A prospective follow-up approach would have revealed diagnostic and pharmacological changes over the course of the patient's hospital stay. A longitudinal approach would have allowed us to detect any significant changes on the weight, serum lipids and glucose levels associated with the initiation of different AP agents. A cross-sectional approach is susceptible to different forms of bias. In particular, the presence of bias by indication, as obese or diabetic patients might be receiving an AP agent that would have a lower risk for the development of metabolic syndrome due to their weight or health status.

In addition, prescribing patterns are affected by local formulary constraints as well as local practice preferences. Our findings represent the AP prescription choices of a relatively small number of prescribers. In order to have more generalizable findings, the inclusion of several hospitals in different geographic areas across the United States would be needed.

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AP3T01. Demographic and Other Sample Characteristics, (N= 224)

Col	Gender	
01	Female	0.3
02	Male	0.7
03	Age (years) Mean (SE)	40.24 (0.99)
04	Ethnicity	
05	White	0.7
06	Non-White	0.3
07	Body Mass Index (kg/m2) Mean (SE)	30.04 (0.43)
08	Body Mass Index	
09	Normal: 18.5 - 24.9 kg/m2	0.2
10	Overweight: 25 - 29.9 kg/m2	0.3
11	Obese: >= 30 kg/m2	0.4
12	Length of Stay (days) Mean (SE)	309.8 (02)
	Row	01

AP3T02. Laboratory Values Sample (N= 224)

Col		
	SERUM CHOLESTEROL AND LIPOPROTEINS	
01	Total Cholesterol mg/dl	178.48 (2.5)
02	> 240 mg/dl	8.79%
03	LDL Cholesterol mg/dl	102.59 (2.14)
04	Less than 100 mg/dl	76.62%
05	Above Optimal 100-129 mg/dl	16.88%
06	Borderline High 130-159 mf/dl	4.55%
07	Very High: >190 mg/dl	1.95%
08	HDL Cholesterol mg/dl	44.7 (0.98)
09	< 40 mg/dl Males/ < 50 mg/dl Females	48.15%
10	SERUM GLUCOSE AND HGBA1C	
11	Fasting Plasma Glucose mg/dl	100.25(2.16)
12	Fasting Plasma Glucose > 100 mg/dl	29.36%
13	Fasting Plasma Glucose > 126 mg/dl	11.01%
14	Fasting Plasma Glucose > 200 mg/dl	4.46%
15	Hemoglobin A1C %	5.66 (0.06)
16	Hemoglobin A1C <= 5.7	77.32%
17	Hemoglobin A1C 5.7-6.4%	15.46%
18	Hemoglobin A1C >=6.5%	7.22%
19	LIVER FUNCTION TESTS	
20	ALT- Alanine Aminotransferase U/L	24.98 (1.41)
21	ALT > 29 U/L	24.77%
22	AST- Aspartate Aminotransferase U/L	22.69 (1.22)
23	AST > 35 U/L	7.34%
	Row	01

AP3T03. Prevalence of Different Psychiatric Disorders (N= 224)

Col	Psychiatric Disorder Group	# Individuals Affected	Prevalence Proportion	SE
01	Schizophrenia and Other Psychotic Disorders	162	0.72	0.03
02	Bipolar Disorders	22	0.10	0.02
03	Depressive Disorders	25	0.11	0.02
04	Anxiety and Somatoform Disorders	7	0.03	0.01
05	Substance Abuse Disorders	100	0.45	0.03
06	Personality Disorders	28	0.13	0.02
07	Dementia and Organic Mental DOs	20	0.09	0.02
08	Total # Diagnosed/ Total # Diagnoses	3.64	X	X
09	Burden Psychiatric Disorders in Sample	X	1.63	X
	Row	1	2	3

AP3T04. Comorbidities Schizophrenia (N=162)

Col	Schizophrenia and Depression	
1	Schizophrenia w/o Depression	93.83 %
2	Schizophrenia w/ Depression	6.17%
3		
4	Schizophrenia and Substance Abuse	
5	Schizophrenia w/o Substance Abuse	56.79%
6	Schizophrenia w/ Substance Abuse	43.21%
	Row	1

AP3T05. Total # Diagnoses, Total # Comorbidities and Comorbidity to Diagnosis Ratio (N= 224)

Row		Schizoph Psych DO	Bipolar Disorders	Depress Disorders	Anxiety Somat DO	Sub Abuse DO	Person DO	Dementia Mental DO	Total # Comorbidities
01	Schizophrenia and Other Psychotic Disorders	N/A	0	10	3	70	11	10	104
02	Bipolar Disorders	0	N/A	0	1	15	6	3	25
03	Depressive Disorders	10	0	N/A	1	10	5	3	29
04	Anxiety and Somatoform DO	3	1	1	N/A	3	2	0	10
05	Substance Abuse Disorders	70	15	10	3	N/A	12	5	115
06	Personality Disorders	11	6	5	2	12	N/A	1	37
07	Dementia and Org Mental DO	10	3	3	0	5	1	N/A	22
08	Total # Comorbidities	104	25	29	10	115	37	22	342
09	Total # Diagnoses	162	22	25	7	100	28	20	364
10	Comorbidity/ Diagnosis Inflation Ratio (CDIR)	0.64	1.14	1.16	1.43	1.15	1.32	1.10	0.94
11	Standardized CDIR	0.68	1.21	1.23	1.52	1.22	1.41	1.17	1.00
	Column	01	02	03	04	05	06	07	08

AP3T06A. Diagnoses by Diagnostic Strata (N= 224)

Row		No Diag DG0	One Diag DG1	Two Diag DG2	Three Diag DG3	Four Diag DG4	Total
01	Schizophrenia and Other Psychotic Dos	0	69	82	11	0	162
02	Bipolar Disorders	0	3	14	4	1	22
03	Depressive Disorders	0	5	11	9	0	25
04	Anxiety Disorders	0	1	3	2	1	7
05	Substance Abuse Disorders	0	5	76	18	1	100
06	Personality Disorders	0	3	14	10	1	28
07	Dementia and Other Organic Dos	0	4	10	6	0	20
08	# Diagnoses in Each Diagnostic Group	0	90	210	60	4	364
09	# Individuals in Each Diagnostic Group	0	90	105	20	1	216
10	# Individuals in Each DG	8	90	105	20	1	224
	Columns	01	02	03	04	05	06

AP3T06B. Diagnoses by Diagnostic Strata in Row Proportions (N= 224)

Row		No Diag DG0	One Diag DG1	Two Diag DG2	Three Diag DG3	Four Diag DG4	Total
01	Schizophrenia and Other Psychotic Dos	0.000	0.426	0.506	0.068	0.000	1.000
02	Bipolar Disorders	0.000	0.136	0.636	0.182	0.045	1.000
03	Depressive Disorders	0.000	0.200	0.440	0.360	0.000	1.000
04	Anxiety Disorders	0.000	0.143	0.429	0.286	0.143	1.000
05	Substance Abuse Disorders	0.000	0.050	0.760	0.180	0.010	1.000
06	Personality Disorders	0.000	0.107	0.500	0.357	0.036	1.000
07	Dementia and Other Organic Dos	0.000	0.200	0.500	0.300	0.000	1.000
08	# Diagnoses in Each Diagnostic Group	0.000	0.247	0.577	0.165	0.011	1.000
09	# Individuals Diagnosed in Each DG	0.000	0.417	0.486	0.093	0.005	1.000
10	# Individuals in Each Diagnostic Group	0.036	0.402	0.469	0.089	0.004	1.000
	Columns	01	02	03	04	05	06

AP3T07. Unadjusted and Adjusted # Diagnoses and Comorbidities, Diagnostic and Comorbidity Inflation Ratios (N= 224)

Row		Unadjusted # Diagnoses	Adjusted # Diagnoses	Remainder Porportion Post Adjustment	Diagnostic Inflation Ratio (DIR) (Unadj/ Adj)	Standardized DIR Adjusted (to Total DIR Sample)	Unadj # Com	Comorb Inflation Ratio (CIR) Adj Diag/ Comorb	Standardized CIR (Adjusted To CIR Total Sample)
01	Psychotic Disorders	162	113.67	0.70	1.43	0.85	266	2.34	0.72
02	Bipolar Disorders	22	11.58	0.53	1.90	1.13	47	4.06	1.24
03	Depressive Disorders	25	13.50	0.54	1.85	1.10	54	4.00	1.22
04	Anxiety Disorders	7	3.42	0.49	2.05	1.22	17	4.98	1.52
05	Substance Abuse Disorders	100	49.25	0.49	2.03	1.20	215	4.37	1.34
06	Personality Disorders	28	13.58	0.49	2.06	1.22	65	4.79	1.46
07	Dementia and Other Organic DO	20	11.00	0.55	1.82	1.08	42	3.82	1.17
08	# Diagnoses in Each Group	Total # Unadj Diag 364	Total # Adj Diag 216.00	Post Adj Prop Whole Sample 0.59	DIR Whole Sample 1.69	1.00	Unadj # Com Whole Sample 706	CIR Whole Sample 3.27	1.00
	Columns	01	02	03	04	05	06	07	08

AP3T08. Analysis on the Distribution of Diagnoses by Diagnostic Groups (N= 224)

Row	Condition	Chi^2	Fischer's Exact Test
01	Schizophrenia and Other Psychotic Dos	0.000*	0.000*
02	Bipolar Disorders	0.373	0.271
03	Depressive Disorders	0.099	0.129
04	Anxiety Disorders	0.018*	0.088
05	Substance Abuse Disorders	0.000*	0.000*
06	Personality Disorders	0.029*	0.023*
07	Dementia and Other Organic Dos	0.457	0.461
	Columns	01	02

AP3T09. List of Antidepressant Agents Prescribed (N= 224)

Col	Medication	# Pat Rx	Median Dose (mg)	Mean Dose (mg)	SE(Mean Dose)
1	Amitriptyline	1	50	50	N/A.
2	Bupropion	12	300	281.25	34.15
3	Citalopram	18	25	36.94	11.3
4	Clomipramine	N/A	N/A	N/A	N/A
5	Doxepin	1	50	50	N/A
6	Duloxetine	3	90	80	26.46
7	Fluoxetine	15	20	26.67	2.87
8	Fluvoxamine	2	100	100	N/A
9	Mirtazapine	16	22.5	27.19	3.68
10	Paroxetine	4	20	20	N/A
11	Sertraline	15	150	135	14.39
12	Trazodone	45	100	168.33	38.44
13	Venlafaxine	13	225	195.19	13.17
	Row	01	02	03	05

AP3T10. List of Mood Stabilizer Agents Prescribed (N= 224)

Col	Medication	# Pat Rx	Median Dose (mg)	Mean Dose (mg)	SE(Mean Dose)
1	Carbamazapine	4	700	675	110.87
2	Gabapentin	15	1200	1366.67	196.56
3	Lamotrigine	13	200	238.46	51.08
4	Lithium	23	900	963.04	90.14
5	Oxcarbazepine	6	1050	1083.33	235.82
6	Topiramate	14	175	162.5	17.53
7	Valproate	49	1250	1351.02	96.39
8	Zonisamide	2	200	200	100
	Row	01	02	03	04

AP3T11. List of Antipsychotic Agents Prescribed (N= 224)

Col	Medication	# Pat Rx	Median Dose (mg)	Mean Dose (mg)	SE(Mean Dose)
1	Aripiprazole	17	10	13.77	2.19
2	Chlorpromazine	8	175	193.75	31.96
3	Clozapine	37	350	313.18	26.00
4	Fluphenazine	11	15	23.18	4.59
5	Haloperidol	35	12	15.57	2.83
6	Haloperidol Decanoate	17	150	145.7	15.34
7	Loxapine	4	50.5	81.75	53.15
8	Lusaridone	1	80	80	.
9	Olanzapine	52	20	19.57	1.46
10	Perphenazine	5	28	27.6	9.30
11	Quetiapine	41	400	418.90	37.83
12	Risperidone	47	4	4.88	0.40
13	Risperidone Depot	6	100	95.83	4.17
14	Risperidone	47	4	4.88	0.40
15	Thiothixene	2	20	20	10
16	Ziprasodone	1	160	160	.
	Row	01	02	03	05

Note: Haloperidol Used by 47 patients / Risperidone Used by 50 patients

AP3T12. Polypharmacy Table Number of Polypharmacy, Polypharmacy to Prescription Ratio (N= 224)

Row	Medication	Aripiprazole	Chlorpromazine	Clozapine	Fluphenazine	Haloperidol	Loxapine	Lusaridone	Olanzapine	Paliperidone	Perphenazine	Quetiapine	Risperidone	Thiothixene	Ziprasodone	Total Conc Rx
01	Aripiprazole	N/A	0	1	0	1	0	0	2	0	0	2	1	0	0	7
02	Chlorpromazine	0	N/A	1	2	1	0	1	2	0	0	1	1	0	0	9
03	Clozapine	1	1	N/A	2	6	0	0	3	0	0	5	2	0	0	20
04	Fluphenazine	0	2	2	N/A	0	0	0	2	0	0	3	2	0	0	11
05	Haloperidol	1	1	6	0	N/A	1	0	10	0	0	6	6	1	0	32
06	Loxapine	0	0	0	0	1	N/A	0	2	0	1	0	1	0	0	5
07	Lusaridone	0	1	0	0	0	0	N/A	0	0	0	0	0	0	0	1
08	Olanzapine	2	2	3	2	10	2	0	N/A	0	1	7	8	1	0	38
09	Paliperidone	0	0	0	0	0	0	0	0	N/A	0	0	0	0	0	0
10	Perphenazine	0	0	0	0	0	1	0	1	0	N/A	0	0	0	0	2
11	Quetiapine	2	1	5	3	6	0	0	7	0	0	N/A	7	0	0	31
12	Risperidone	1	1	2	2	6	1	0	8	0	0	7	N/A	0	0	28
13	Thiothixene	0	0	0	0	1	0	0	1	0	0	0	0	N/A	0	2
14	Ziprasodone	0	0	0	0	0	0	0	0	0	0	0	0	0	N/A	0
15	# Total Concomitant Rx	7	9	20	11	32	5	1	38	0	2	31	28	2	0	186
16	# Primary Rx	17	8	37	11	47	4	1	52	0	5	41	50	2	1	276
17	Conc/ Primary Rx Ratio	0.41	1.13	0.54	1.00	0.68	1.25	1.00	0.73	0	0.40	0.76	0.56	1.00	0.00	0.67
18	Standardized CPR	0.61	1.67	0.80	1.48	1.01	1.85	1.48	1.08	0	0.59	1.12	0.83	1.48	0.00	1.00
	Column	01	02	03	04	05	06	07	08	09	10	11	12	13	14	15

AP3T13. Indicators of Antipsychotic Use (N= 224)

Row	*Use Indicator*	*# Pts*	*Prop Pts*
1	*Total # of Antipsychotics Orders*	*276*	*N/A*
2	*Total # Typical Antipsychotic Orders*	*77*	*N/A*
3	*Total # Atypical Antipsychotic Orders*	*199*	*N/A*
4	*Total # Depot Antipsychotic Orders*	*23*	*N/A*
5	*Patients Prescribed at Least One AP*	*194*	*0.87*
6	*Patients Prescribed at Least Two AP*	*72*	*0.32*
7	*Patients Prescribed Atypical AP*	*164*	*0.73*
8	*Patients Prescribed Depot Antipsychotics*	*22*	*0.10*
	Column	*01*	*02*

AP3T14. Indicators of Mood Stabilizer and Antidepressant Use (N= 224)

Row	Use Indicator	# Pts	Prop Pts
1	Total # of Mood Stabilizer Orders	126	N/A
2	Patients Prescribed Mood Stabilizers	106	0.47
3	Total # of Antidepressant Orders	100	N/A
4	Patients Prescribed Antidepressants	84	0.38
	Column	01	02

AP3T15. Indicators of Medication Combinations Use (N= 224)

Row	Use Indicator	# Pts	Prop Pts
1	Antipsychotic Agent + Mood Stabilizer	82	0.36
2	Antipsychotic Agent + Antidepressant	70	0.31
	Column	01	02

AP3T16. Indicators of Metabolic Syndrome and Prediabetes in the Sample

Plasma Triglyceride Level >150 mg/dl
Plasma High Density lipoprotein (HDL) Level: <40 mg/dl in Males *<50 mg/dl in Females*
Fasting Serum Glucose Level >100 mg/dl
Body Mass Index (BMI) >30 kg/m^2
Hemoglobin A1C > 5.7%

AP3T17. Number of Prescriptions Stratified by Prescription Group and Totals (N=224)

Row	Medication	PG0	PG1	PG2	PG3	PG4	Totals
01	Aripiprazole	0	12	4	0	1	17
02	Chlorpromazine	0	2	3	3	0	8
03	Clozapine	0	17	20	0	0	37
04	Fluphenazine	0	2	7	2	0	11
05	Haloperidol	0	20	22	5	0	47
06	Loxapine	0	1	1	2	0	4
07	Lusaridone	0	0	1	0	0	1
08	Olanzapine	0	22	23	6	1	52
09	Paliperidone	0	0	0	0	0	0
10	Perphenazine	0	4	0	1	0	5
11	Quetiapine	0	16	20	4	1	41
12	Risperidone	0	25	23	1	1	50
13	Thiothixene	0	0	2	0	0	2
14	Ziprasodone	0	1	0	0	0	1
15	Total # Prescriptions	0	122	126	24	4	276
16	Total # Individuals Prescribed	0	122	63	8	1	194
17	Total # Individuals	30	122	63	8	1	224
	Column	01	02	03	04	05	06

AP3T18. Prescriptions Stratified by Prescription Group by Row Percentage (N=224)

Row	Medication	PG0	PG1	PG2	PG3	PG4	Totals
01	Aripiprazole	0.00	70.59	23.53	0.00	5.88	100.00
02	Chlorpromazine	0.00	25.00	37.50	37.50	0.00	100.00
03	Clozapine	0.00	45.95	54.05	0.00	0.00	100.00
04	Fluphenazine	0.00	18.18	63.64	18.18	0.00	100.00
05	Haloperidol	0.00	42.55	46.81	10.64	0.00	100.00
06	Loxapine	0.00	25.00	25.00	50.00	0.00	100.00
07	Lusaridone	0.00	0.00	100.00	0.00	0.00	100.00
08	Olanzapine	0.00	42.31	44.23	11.54	1.92	100.00
09	Paliperidone	N/A	N/A	N/A	N/A	N/A	N/A
10	Perphenazine	0.00	80.00	0.00	20.00	0.00	100.00
11	Quetiapine	0.00	39.02	48.78	9.76	2.44	100.00
12	Risperidone	0.00	50.00	46.00	2.00	2.00	100.00
13	Thiothixene	0.00	0.00	100.00	0.00	0.00	100.00
14	Ziprasodone	0.00	100.00	0.00	0.00	0.00	100.00
15	Total # Prescriptions	0.00	44.20	45.65	8.70	1.45	100.00
16	Total # Individuals Prescribed	0.00	62.89	32.47	4.12	0.52	100.00
17	Total # Individuals	13.39	54.46	28.13	3.57	0.45	100.00
	Column	01	02	03	04	05	06

AP3T19. Adjusted Number of Prescriptions Stratified by Prescription Group (N=224)

Row	Medication	Unadjusted Number Rx	Adjusted Number Rx	Remainder Rx Prop After Adj	Polypharm Ratio (PR)	Standardized PR
01	Aripiprazole	17.00	14.25	0.84	1.19	0.84
02	Chlorpromazine	8.00	4.50	0.56	1.78	1.25
03	Clozapine	37.00	27.00	0.73	1.37	0.96
04	Fluphenazine	11.00	6.17	0.56	1.78	1.25
05	Haloperidol	47.00	32.67	0.70	1.44	1.01
06	Loxapine	4.00	2.17	0.54	1.85	1.30
07	Lusaridone	1.00	0.50	0.50	2.00	1.41
08	Olanzapine	52.00	35.75	0.69	1.45	1.02
09	Paliperidone	N/A	N/A	N/A	N/A	N/A
10	Perphenazine	5.00	4.33	0.87	1.15	0.81
11	Quetiapine	41.00	27.58	0.67	1.49	1.04
12	Risperidone	50.00	37.08	0.74	1.35	0.95
13	Thiothixene	2.00	1.00	0.50	2.00	1.41
14	Ziprasodone	1.00	1.00	1.00	1.00	0.70
15	Total Number	Total # Unadj Rx: 276.00	Total # Adj Rx: 194.00	Remainder Prop Total: 0.70	PIR Total Sample: 1.42	1.00
	Column	01	02	03	04	05

AP3T20. Indicators of Metabolic Syndrome in Schizophrenia Patients with and without Substance Abuse Comorbidity (N= 162)

Row		Schizophrenia w/o Sub Abuse (N=92) (%)	Schizophrenia with Sub Abuse (N =70) (%)	P-Value
01	Triglyceride Level >150 mg/dl	59.78	44.29	0.058
02	High Density lipoprotein (HDL) Level: M <40 mg/dl/ F: <50 mg/dl	45.98	56.72	0.186
03	Fasting Serum Glucose Level >100 mg/dl	28.41	32.35	0.594
04	Body Mass Index (BMI) >30 kg/m^2	43.48	44.29	0.918
05	Hemoglobin A1C > 5.7%	34.15	20.00	0.064
06	Metabolic Score (Mean (SE))	2.30(0.15)	1.93(0.17)	0.119
07	Metabolic Score Higher than Median	48.91	55.71	0.391
	Column	01	02	03

AP3T21. Indicators of Metabolic Syndrome in Schizophrenia Patients by Number of Antipsychotic Agents Prescribed (N= 162)

Row		Pts Receiving ≤ 1 AP Agent (N =152) (%)	Pts Receiving ≥ 2 AP Agents (N=72) (%)	P-Value
01	Triglyceride Level >150 mg/dl	46.71	51.39	0.513
02	High Density lipoprotein (HDL) Level: M <40 mg/dl/ F: <50 mg/dl	49.32	45.59	0.610
03	Fasting Serum Glucose Level >100 mg/dl	32.21	23.19	0.173
04	Body Mass Index (BMI) >30 kg/m^2	51.39)	44.64	0.162
05	Hemoglobin A1C > 5.7%	28.68	16.92	0.073
06	Metabolic Score (Mean (SE))	2.12 (0.12)	1.88 (0.16)	0.244
07	Metabolic Score Higher than Median	48.68	62.50	0.053
	Column	01	02	03

AP3T22. Antipsychotic Prescription Patterns in Schizophrenia Patients with and without Substance Abuse Comorbidity (N= 162)

Row		Schizophrenia w/o Sub Abuse (N=92) (%)	Schizophrenia with Sub Abuse (N =70) (%)	P-Value
01	Receiving One or More AP Agent	90.22	100.00	0.007*
02	Receiving Two or More AP Agents	33.70	42.86	0.233
03	Use of Atypical AP Agents	76.09	80.00	0.553
04	Receiving Only Typical AP Agents	14.13	20.00	0.321
05	Receiving Long Term IM AP Agents	10.87	14.29	0.513
06	Receiving Antidepressant Agents	34.78	24.29	0.150
	Column	01	02	03

CURRICULUM VITAE

RUBEN MIOZZO, MD MPH

Address and Telephone
8 Childs Street
Shrewsbury, MA 01545
Phone: 508-797-2031
Emails: rmiozzo1@jhmi.edu;
Ruben.Miozzo@umassmed.edu

Education

March 1984 – December 1989	*School of Medicine,* *University of Buenos Aires, Argentina. Medical Doctor.*
June 1990 – May 1994	*José Borda Hospital, Buenos Aires. School of Medicine, University of Buenos Aires.* *Residency in Psychiatry.*
June 1993 - September 1996	*School of Medicine, University of Buenos Aires.* *Post-Doctoral Specialist Degree in Psychiatry*
July 1997 – June 1998	*State University of New York at Stony Brook.* *First Post Graduate Year: Residence in Psychiatry.*
July 1998 – June 2001	*Beth Israel Medical Center. Albert Einstein College of Medicine* *Second to Fourth Post Graduate Year: Residency in Psychiatry*
August 2001- June 2010	*University of Massachusetts Medical School* *Assistant Professor of Psychiatry* *Lecturer/ Clinical Supervisor of Residents and Medical Students*
August 2002- June 2005	*School of Public Health and Health Sciences at the University of Massachusetts Amherst*
August 2010- Present	*Graduate Training Program in Clinical Investigation* *Johns Hopkins University School of Medicine &* *Johns Hopkins Bloomberg School of Public Health* *PhD Candidate Clinical Investigation Program*

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